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HOW TO BECOME A CARDIOVASCULAR INVESTIGATOR

Symposium Presentations

I. CHOOSING A RESEARCH PROJECT/MENTOR

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How can you find someone who will help you achieve your research goals? The first priority is to know yourself and your area of research interest. There is no correct timetable for this; it really has to do with where you are in your own internal sorting-out process and career development. Once it is time to choose a mentor to help you explore your interests or to make a transition into a new research area, there are key questions to address.

Choosing a mentor. The process of selecting a mentor is a reverse interview process. After a lifetime of being interviewed for jobs or academic programs, the tables are turned and now you orchestrate the interview. Remember that young investigators usually end up doing work in their mentor's area of expertise first. Therefore, make sure you have real interest in the research being done by your prospective mentor's laboratories or research program because you will be focusing on these.

What is a mentor? Mentor was a friend of Ulysses in the *Odyssey*. In fact, in the story the goddess Minerva assumes the form of Mentor when she accompanies Telemachos to search for his father because Mentor was so respected as a wise, faithful, and trustworthy counselor to Ulysses. This is a good starting list of important traits to look for in a mentor. When starting the process of choosing a mentor, I recommend that cardiology fellows meet with at least two and preferably three potential mentors. Do not make a snap decision. Begin to meet potential mentors no later than the first four months of your second year of fellowship if you are on the traditional fellowship trajectory. Set up meetings with potential mentors and sit down with them to talk about what they do in their research programs. Above all else, pay attention to the personal interaction as you begin to know potential mentors. Is this a person you can feel good about working with for an extended period of time? Does the "chemistry" between you feel right?

Go ahead and talk about the specific research question you are especially interested in, but remember: because of the way science is done today, it is often a team effort. As a result of the enormous sophistication being brought to bear on research questions in all areas, the mentors you interview are going to have established research efforts that are intricate and well developed. So, be sure you like a potential mentor's area of interest as much as you like the person.

Obtain copies of papers that are representative of the mentor's work. If a paper has been submitted and is under review, ask if you can have a copy of it to get a sense of what is currently happening in their program. Keep it confidential, but take it home, read it, and think about it. Is it boring? Is it the best thing you have read since *The Godfather*? Try to understand whether there is some intrinsic appeal to you in the scientific area being investigated by a potential mentor. Whether it is a study of brachial vasomotion and endothelial function in outpatients, culling an existing dataset using outcomes research methods, or cloning a protein and understanding how it works to regulate blood vessel cell function—does it match your interests? No matter how much you like a person, if they have nothing going on in your true field of interest, reconsider that person's value to you as a mentor.

Ask potential mentors how often they meet with trainees. How often are their laboratory meetings? Ask how often you will personally meet with your mentor. I have a laboratory meeting once a week on Thursday mornings and spend the rest of Thursday meeting individually with trainees, and this schedule is something I try very hard to protect.

Have potential members describe the structure in their laboratory environment. Whether it is an outpatient clinical laboratory or a bench laboratory does not matter. Are you going to work side by side with the mentor? That is unusual unless it is someone who is more junior, but it may be preferable to you. Will you be assigned to someone who is several years more advanced than you who is spearheading a project, and will that person become your day-to-day mentor? If that is the case, you need to also meet that individual.

What is the lab like? Is it a big lab? Are there other fellows in the lab? Are there other fellows expected to join the lab soon or perhaps at the same time you will be joining? If there are people who have been through the lab, try to speak with them and ask them what the experience was like. Is it mostly a postdoctoral laboratory? Is it filled with international fellows or fellows from within the U.S.? Is it mostly undergraduate and graduate students? What is the mix? Where is the lab located? Is it in proximity to the clinical division, where you want to be able to attend seminars and conferences that are offered? Is it in proximity to where you will see patients in an outpatient clinic setting?

What is going to be expected of you by your prospec-

tive mentor? What will they want from you? That is often a very revealing question. If the answer to that question is, "I need you to be sure my coffee is here every morning and then we will talk," . . . well, enough said! If you know your prospective mentor is interested in you having an intense educational experience that will be fun, that is a good start. Be very frank about your own stage and interests by stating clearly, "I am not sure I want to do research," or "I am passionate about research." Bring into the mix what you are really thinking. This is about what you want, not what you think other people want from and for you.

In our research center, there is a mentoring or teaching relationship at every step, and they differ. The center director and co-director have a different form of mentoring relationship than the one that postdoctoral fellows have with individual principal investigators; the predoctoral students and college and high-school students receive an enormous amount of mentoring and teaching from everyone in the laboratory. So, the opportunity for you to practice being a mentor is also part of the process.

An important part of your experience should include training in the legal and ethical aspects of conducting research, including data management, as well as publication practices, and authorship, including the world of peer review and privileged information. You should learn about collaborations, human subjects' research, and conflicts of interests. Mentors should review with you the handling of research data, including the collection and recording of primary data as well as what is required in terms of annotating and indexing laboratory data. Today, a lot of this may be computerized. Research data are legal documents. It is important to learn about these issues and their implications. Also, ask about the retention of your data and where it is stored when you are done working on the project. Can you have copies to take with you? If you spend three years of your life doing something and then join the faculty somewhere else, this will likely be important to you. Data management is important. It can be laborious, but investigators have to know how to take, record, and keep data. That includes an understanding of whom the data belong to, where data will be stored, how data will be processed, and what are considered good data-keeping practices. A mentor-to-be should be able to explain how these important matters will be learned.

Other mentoring issues. Accessibility to your mentor is a critical issue. If a mentor says, like the old *New Yorker* cartoon, "No, Thursday is out. How about never? Is never good for you?" this is not the person you want for a mentor. You want to be able to call and say, "I just wrote my first grant and have incorporated your comments—could you look at it again?" The response should be: "Sure."

Is the potential mentor someone who will listen attentively? Is the person interested in your self-sufficiency? I like very much this quote from a professor of mine in undergraduate school. I went to Amherst College and my political science professor, George Kateb, who is quite a brilliant teacher and is now a professor at Princeton, said something I will never forget it. He paused one day in the middle of a lecture while talking about the process of teaching. He looked up at us and said, "You know, it's the purpose of a good teacher to make himself obsolete." I have never forgotten that comment; it is a great definition to bear in mind when choosing a mentor.

Does the potential mentor have good interpersonal skills? This is key. Is the mentor unlikely to be ruffled by your success and become competitive with you? That is not an inconsequential issue; it is a sad issue, frankly, but it needs to be brought up because there are insecure people everywhere and they do not make good mentors very often. The last thing you want is to develop an area of expertise and then to have your mentor's name appearing on your paper for the next decade when you finish training. Likewise, you do not want to be working in an area and have a mentor who continues publishing papers that are competing directly with what you want to do. That is a sensitive issue and conversation, but it is one you ought to have early on. Carve out an area of research as you mature and define your research and career goals. A good mentor, in the process of making him or herself "obsolete," ought to be able to look you in the eye and say, "I'm going to stay out of that area. In fact, when it comes to that one paper that's really transitional, my bias is going to be to take my name off." That is the goal and the hope: a mentor who really helps launch your independent career.

Another good quote is from Bishop Stephen Neill (1): "The bad teacher imposes his ideas and his methods on his pupils and such originality as they may have is lost in the second-rate art of imitation." You have to be encouraged and emboldened to be creative. Granted, sometimes you are going to have research ideas that are a bit "whacky." In the beginning, such ideas are part of learning and being creative. A mentor's job is to gently say, "That's kind of peripheral. Let's bring it closer to some of the issues you were talking to me about earlier." Having said that, do not be pigeonholed or discouraged from exploring that which excites you. You are certainly not there to become the mouthpiece of someone whose work is already well established; you are there to benefit from the process and environment. Of course, you will become a representative of the work you do together with your mentor, at least in regards to those issues that are germane to the science you are doing together, but that is very different. You need to be allowed to be original and creative and to differentiate.

When choosing a mentor, consideration also must be given to the financial support you will be provided. If you are learning at the bench, you need to know that at least two years of work will be supported if you are already experienced and three years of work will be supported if you are

Table 1. Research Training Websites

http://www.nih.gov/NIH homepage
http://www.training.nih.gov/handbook/
http://www2.nas.edu/cosepup
The Committee on Science, Engineering, and Public Policy's (COSEPUP) homepage
http://www.nextwave.org
American Association for the Advancement of Science (AAAS) *Science's NextWave*
http://www2.nas.edu/cpc
National Research Council's *Career Planning Center for Beginning Scientists and Engineers* (CPC)

From www.nhlbi.nih.gov/funding/training/redbook/trainslides.ppt.

not already experienced. In other words, ideally support should be provided to you without your having to write a grant. You may want to write a grant, but you should not have to obtain a grant in order to receive a full training experience.

If you are learning clinical research, I strongly urge you to consider a didactic training course in statistics, epidemiology, outcomes, trial methods, and so forth. Summer courses in these areas are often offered by some of the better programs; if this is not available at your institution, will the prospective mentor support your going somewhere to take such a course? It is a wonderful investment in your future.

Conclusions. There are many research training websites and I encourage you to peruse them (Table 1). There are also a number of National Heart, Lung, and Blood Institute (NHLBI) research training programs for postdoctoral individuals, including programs for minorities and disabled researchers (Table 2).

Educator Amos Bronson Alcott (1799–1888) said: "The true teacher defends his pupils against his own personal influence. He inspires self-distrust. He guides their eyes from himself to the spirit that quickens him. He will have no disciple." In other words, you should not become a clone of your mentor (2).

But, perhaps Albert Einstein (1879–1955) said it best: "It is the supreme art of the teacher to awaken joy and creative expression and knowledge" (3).

Question and Answer

Question: For fellows who are considering working with a preceptor who has a private interest or a financial interest in the work, what are some of the questions or concerns to be addressed before getting involved in a project?

Dr. Mendelsohn: That is a complicated question. I would begin by asking a trainee why he or she would want to get involved in something like that at this point in their training. Unless the trainee is seeking training in the business/industry side of research, I would caution against that. On the other hand, for example, if the trainee is one of the MD/MBA students we have at our institution, then this is exactly what they might want to pursue. In that case, there are specific questions relating to who owns the technology.

Table 2. NHLBI Postdoctoral Programs

Postdoctoral programs for all individuals:
• NIH Summer Employment Program
• Individual Postdoctoral National Research Service Award (F32)
• Institutional National Research Service Award (T32)
• Intramural Research Training Award
• Staff Fellowship Program*
• Institutional National Research Service Award in Sleep Research (T32)
Postdoctoral programs for underrepresented individuals:
Minority scientists
• Minority Institutional Research Training Program (T32)
• Minority Access to Research Careers (F34)
• Research Supplements for Underrepresented Minority Individuals in Postdoctoral Training
Scientists with disabilities
• Research Supplements for Individuals with Disabilities in Postdoctoral Training
Awards for new researchers:
• Mentored Clinical Scientist Development Award (K08)
• Independent Scientist Award (K02)
• Career Transition Award (K22)
• Mentored Patient-Oriented Research Career Development Award (K23)
• Mentored Quantitative Research Career Development Award (K25)
Awards for minority scientists and researchers with disabilities:
Minority researchers
• NHLBI Minority Institution Research Scientest Development Award (K01)
• NHLBI Mentored Minority Faculty Development Award (K01)
• Research Supplements for Underrepresented Minority Investigators
Researchers with disabilities
• Research Supplements for Investigators with Disabilities Developing Independent Research Careers

*Performed at the NIH.

What will happen if new technologies are discovered along the way? What rights, if any, will evolve for the mentor, the school/university, and so on?

Question: Should a mentor be someone involved in the field in which you want to do research? Sometimes you can not find such a person in your own university, especially in translational science research. Do you recommend we look all over the country and find somebody outside the institution you are working in and try making them a mentor? Or are we pretty much restricted to our own university?

Dr. Mendelsohn: That depends on the stage you are at in training. To make the analogy to graduate students, before doing a thesis, a graduate student often does rotations in different laboratories before selecting a mentor. So, there are two separate approaches to your question. One would be to visit a number of different centers for a short time and at least get a sense of what is going on. But if, as I think your question implies, you are ready and the best person in your mind to work with you is not at your campus, then what do you do? I feel very strongly that you should go to the best laboratory you can and work there. Many training programs support that: go off site as needed.

Question: What is more important when choosing a mentor: the mentor's area of research or the tools that the mentor is going to provide? Sometimes a mentor is doing work in an area that may not be your first choice, but you know that this mentor will provide you the greatest number of tools you will need to succeed. Because we may change directions later in terms of our specific research interests, what is more important in the training period, the topic or the tools?

Dr. Mendelsohn: I do not think it is the tools. It is the environment. You have to be drawn to the area you are going to work in. You would not want to go study clinical heart failure if really deep down what you want to do is outcomes research in electrophysiology. Certainly, once you have chosen an area, many state-of-the art tools are going to be available to you if it is a good laboratory or a good research program. Most young people who come to the laboratory can learn almost any methodology in a week. That is not the issue. The issue is asking the right research questions, and learning to do this comes with the right environment.

Dr. Fuster: It is very common to think that mentors come from the skies to you and, if they do not, you think there are no mentors. What Dr. Mendelsohn said is extremely important; you really have to go after mentors yourself. You interview them. If you do not, there are no mentors, because all of us are very busy and we are not likely to turn to you and say, "You look good to me. Let me mentor you." It is unfortunate because many people think there are no mentors in their institution. But did you ask? Did you go after them and read their papers? This is what Dr. Mendelsohn is talking about, and this is very important.

There is also the concept of the person who really advises you in your career, in general, not in specific projects. Such a general mentor is absolutely critical. Again, it is based on experience. One of the great problems is getting a mentor for specific research, but there is nobody around you who really guides your career in a more general sense. Maybe you do not belong there, you are really not in the right place, and you need someone who can look at your situation and help you see that. So, I am emphasizing the general individual who really knows you, whether that is someone in your own institute or somebody you had some attachment to before. It is very important that you have an individual or individuals who really guide your careers. They must be trustworthy. These are people who really would do anything for you.

Dr. Mendelsohn: I could not agree more. If you are going to be a cardiologist, there are leaders in cardiology at your institutions who are not involved in the specific area you are seeking to work in, but they still may be wonderful mentors in the general sense that Dr. Fuster is describing. These are the people you can bounce ideas off of and say, "You know, I have narrowed my mentor search down to Person X and Person Y. Can you help me think about it?" To have someone who you trust to be available to have that conversation with you is very important.

Dr. Fuster: Here is another issue: what happens after six months when you find that your mentor is not the person you wanted? That is a tough issue, but we see it commonly. In my experience, the first person you choose as a mentor fails 50% of the time. Then what do you do? First, go to the head of the department or division and present the situation. The department or division head should understand the situation, know the involved parties well, and know best how to approach it. Never try to take care of this yourself. Out of the blue, you may say a few words that can be damaging to you in the future. So you have to be very cautious, and this is why you need the advice of people who will give you an overall view of how to proceed. Again, this is a very common problem, and you should be at least ready with some idea of how to approach it.

Dr. Mendelsohn: It is another good reason to have a more general mentor helping "shepherd" you through the process.

Dr. Fuster: In regard to mentoring, classically, you look for mentors who are savvy, often 60 years of age or older, great professors, and people with a lot of experience. Dr. Mendelsohn, do you think these people are practical as mentors in the world we live in today? In general, are the younger generations of researchers, who are much more into what is happening right now in research, better able to be a mentor, although not the general mentor who assists you with the practical issues of a career?

Dr. Mendelsohn: I think that while it may be the purpose of mentors to make themselves obsolete, you do not want them to be already obsolete! Most of the time, the really good senior mentors of the type that you are describing as the "classic" image of a mentor have a cadre of superb, "fire in their belly," next-level investigators who are between the ages of 35 and 50 years, who run substantial programs with their own R01s, and who really are absolutely in the "sweet spot" to be superb mentors for persons at the start of their careers. You are absolutely right; those are the people you want to work for because they are at the center of the most current issues in the field.

II. FUNDING OPPORTUNITIES FOR INVESTIGATORS IN THE EARLY STAGES OF THEIR CAREER DEVELOPMENT

C. William Balke, MD (Office of the Dean, University of Kentucky College of Medicine, Lexington, Kentucky)

The metrics for academic success are salary support from peer-reviewed grants and authorship in publications. Other factors come into play, such as teaching abilities and interpersonal skills, but the bottom line is that those two

Table 3. Sources of Support Information

National Institutes of Health; National Heart, Lung, and Blood Institute (NIH/NHLBI) http://www.nih.gov http://www.nhlbi.nih.gov
K Award Program Announcements — "K Kiosk" http://grants2.nih.gov/training/careerdevelopmentawards.htm
American Heart Association http://www.americanheart.org
American College of Cardiology http://www.acc.org
The Original How to Write a Research Grant Application http://www.niaid.nih.gov/ncn/grants/write/index.htm
Adviser, Teacher, Role Model, Friend: On Being a Mentor to Students in Science and Engineering National Academy Press read online at http://www.nap.edu/readingroom/books/mentor/ or purchase at http://books.nap.edu/catalog/5789.html

metrics are what matter. There are many opportunities to gain credentials in both of these metrics.

There are a number of sources of support (Table 3). One frequently known but underutilized area of support is going directly to the National Heart, Lung, and Blood Institute (NHLBI) or the National Institutes of Health (NIH). The NIH website has a link called the "K Kiosk," which is specifically for training information and awards. The websites for both the American College of Cardiology and the American Heart Association are very user-friendly and contain information for young investigators.

There is additional help available from other underutilized resources (Table 4). Many institutions have institutional NIH K30 or K12 awards, which are designed for clinical research curriculum development and the development of independent clinical scientists. Seek out faculty who have an award that might be suitable for you and then ask them about it. Also, the people at specific institutes at the NIH are very friendly and cooperative. Their goal is to help get the best applications to fund the best science, so the information they have is timely and pertinent.

Loan repayment program. The NIH Loan Repayment Program (Table 4) is an opportunity to get some relief for the loans that have been incurred, both through undergraduate and graduate medical education. The program supports people who are in training for clinical research or basic and clinical pediatric research programs. It is not required that you have your own grant; if you are part of a training program at a university and have a doctoral-level degree, you qualify as a government research-funded individual. This is for individuals with student loan debt equal to 20% or more of your annual salary.

Up until fiscal year 2003, there was approximately a 58% success rate in terms of approved applications for clinical research and 49% for pediatric research.

Training grants are available for individuals with or earning a health-professional doctorate (Fig. 1). Residents often are supported by institutional training grants (T32). Some individuals in the first couple of years of fellowship have the opportunity to be in a fellowship T32 training grant, which is quite an honor because these positions are limited and highly competitive.

National Research Service Award (NRSA) (F32). The NRSA, otherwise known as the F32, is for post-doctoral training within the broad scope of biomedical, behavioral, or clinical research (Table 5). The F32 is an individual version of the T32 that funds you; it is something you apply for as a principal investigator with a mentor's support. It will fund your time during the research activities of your fellowships. Individuals in a four-year cardiology fellowship, with the first two years for clinical work and the last two years devoted to research, be it clinical, basic, or translational, should be applying for these grants in the middle to end of the second year of fellowship, as they will fund you for the last two years. Traditionally, most of these awards go to PhDs. This is not because MDs are not competitive, but rather MDs do not think about them; MDs actually have a competitive advantage to the extent that MDs are underrepresented and they work very hard to review favorably.

If you have finished college and medical school, did your house staff training, and been exposed to other people doing research but you have not done any yourself, that is fine. You can still apply because the experience you are going to get once you receive the award is going to give you that experience. You want to describe the new training experiences that you are going to get and how those experiences are going to broaden your scientific background. In other words, describe your potential to become an important contributor to biomedical, behavioral, or clinical science.

Some of the most important aspects of applying for the

Table 4. Help Along the Way

Mentor(s)
Institutional K30 and/or K12 Award faculty
Current awardees
NIH Program Officer and Study Section Scientific Review Administrator (SRA)
NIH Loan Repayment Programs http://www.lrp.nih.gov
5 programs including clinical research and basic/clinical pediatric research programs
Eligibility requirements • Doctoral-level degree • Government research funding (federal, state, or local) or domestic nonprofit research • Student loan debt ≥20% annual salary • U.S. citizenship or permanent residency • Non-federal government job
NIH pays income tax liability
2-year award with ability to renew for an additional 2-year period
Maximum payment = $35,000/year
NIH "Service Obligation": conduct qualifying research supported by a domestic nonprofit or U.S. government (federal, state, or local) entity for 50% of time (at least 20 h per week based on a 40-h week) for 2 years. NIH makes quarterly loan repayments concurrent with the participants' satisfaction of their service obligation.

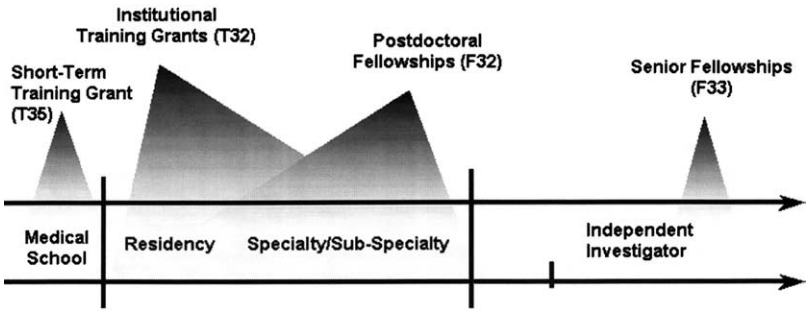

Figure 1. National Research Service Award (NRSA) fellowships and training grants (F & T awards) for individuals with or earning a health professional doctorate. Source: NIH website, http://www.nih.gov.

Table 5. Ruth L. Kirschstein National Research Service Awards (NRSA also known as an F32)

Eligibility requirements
- Citizens or non-citizen nationals of the U.S.
- Permanent residents (Alien Registration Receipt Card I-551)
- Individuals on temporary or student visas are *not* eligible
- Doctoral level degree: PhD, MD, DO, and so on

Candidate
- Previous academic performance
- Previous research experience (if any) and performance
- New training experiences designed to broaden the candidate's scientific background
- Potential to become an important contributor to biomedical, behavioral, or clinical science

Sponsor (mentor) and training environment
- Research qualifications in the area of the project
- Extent and quality of his/her proposed role in guiding and advising the applicant
- Previous experience in training researchers
- History of research productivity and support
- Availability of staff, research support, and facilities for high-quality research training

Research proposal
- Hypothesis driven
- Specific aims: *testable* predictions of the hypothesis
- Preliminary data (if any)
- Research design
  - Scientific soundness
  - Feasibility
- Relationship to the candidate's career development plans

Training potential
- An assessment of the value of the proposed fellowship experience as it relates to the candidate's needs in preparation for a career as an independent researcher

Application receipt dates
- April 5th; August 5th; December 5th

Stipend (2005 schedule)
- $35,568 (0 years since earning degree) to $51,036 (7 or more years of postdoctoral experience) up to 3 years' support

Allowable costs
- Tuition and fees: 100% of 1st $3,000 and 60% of >$3,000
- Institutional allowance: up to $4,400/year
- Other training costs (e.g., travel to remote field sites): up to $3,850

Payback
- One month of payback for each month of training, up to a maximum of 12 months. This requirement can be fulfilled by teaching or research (a minimum of 20 h per week) on a continuous basis, beginning within 2 years after support ends.

F32 award are the sponsor and training environment. Your sponsor or mentor is probably the single greatest determinant of your long-term success as an academic physician. Choosing a mentor wisely is probably the single most important thing you will do as a young investigator, and you should judge your sponsor on specific criteria. When you apply, your mentor will write a statement outlining his or her experience in training researchers. You need to know this information to see if it is worth spending your time with that individual. Clearly, anyone worthy of being your mentor has to be productive in terms of research grant support and publications. Also, you must be in an environment that has the staff, research support, and facilities for high quality research training.

The actual research proposal for the F32 award must be hypothesis-driven and include specific aims, which are testable predictions of your hypothesis. The research proposal should contain preliminary data, if available, although at this stage, most investigators will not have much preliminary data. If you are proposing a clinical project and you are paired with a mentor, you can use preliminary data from his or her studies, noting that this is what the group has done and that you will be adding your own work. The proposal should have a research design, and it should describe how the design relates to your career development plans.

The last element of the F32 application process is training potential: what is the value of this experience over the time period being requested? How will it help you prepare for a career as an independent investigator? It may give you skills. It may give you exposure. It may give you a number of things that will enable you to take the next step. It does not have to be long, but you need to think about the training potential of what you are proposing to do.

K awards. Let us assume you are at the end of your fellowship and you have determined you do not want to go into clinical practice; instead you want to do research. What do you need to make that career goal happen? First, you need the tools and education for clinical or basic science research and you may need some sophisticated training depending on your area of interest. You can use a K award to assist you in designing a program with didactic studies to help you with the clinical or basic science research aspects of your study and then have a mentored clinical research

Table 6. K Awards Available From the National Institutes of Health

K01 Mentored Research Scientist Development Award
Career development in a new area of research. 3 to 5 yrs; salary determined by sponsoring institution.

K02 Independent Scientist Award*
Develop the career of the funded scientist. 5 yrs; 75% effort.

K05 Senior Scientist Award
For outstanding scientists with a sustained level of high productivity. 5 yrs; 75% effort; funding determined by the sponsoring institution

K07 Academic Career Award
Developmental/leadership in academic instruction, research, administration. 2 to 5 yrs; 25%–75% effort; requires institutional sponsorship.

K08 Mentored Clinical Scientist Development Award*
Development of the independent clinical research scientist. 3 to 5 yrs; 75% effort.

K18 Career Enhancement Award for Stem Cell Research*
Supports full- or part-time training in use of human or animal embryonic, adult, or cord blood stem cells. 6 mos to 1 yr.

K22 Career Transition Award*
Support to an individual postdoctoral fellow in transition to a faculty position.

K23 Mentored Patient-Oriented Research Career Development Award*
Development of the independent research scientist in the clinical arena. 3 to 5 yrs; 75% commitment.

K24 Midcareer Investigator Award in Patient-Oriented Research*
Development of clinical mentors conducting funded research. 3 to 5 yrs; 25% to 50% effort.

K25 Mentored Quantitative Research Career Development Award*
To foster interdisciplinary collaboration in biomedical research by supporting career development experiences for scientists with quantitative and engineering backgrounds. 3 to 5 yrs; 75% effort.

K26 Midcareer Investigator Award in Mouse Pathobiology Research
Provides support for established pathobiologists who wish to devote up to 50% of their effort to research and mentoring in the field of mouse pathobiology. 3 to 5 yrs; renewable; 25% to 50% effort.

K30 Clinical Research Curriculum Development
Institutional award for development of a clinical research curriculum.

K12 Mentored Clinical Scientist Development Program Award
Support to an institution for the development of independent clinical scientists.

*Indicates awards available from National Heart, Lung, and Blood Institute.

program with your mentor. The NIH offers a variety of K awards that are institute-specific (Table 6, Fig. 2).

The K awards (K08, K23) (Table 7) bridge the transition for those in the specialty/subspecialty period of training. These awards can be applied for in the last year of fellowship, and they take affect when you get your early faculty position.

From 1999 through 2002, almost 50% of K08 and K23 applications received funding at the NHLBI. Although award rates have fallen with the recent tightening of the NIH budget, the success rate of K-award applications remains significantly better than the traditional NIH investigator-initiated awards (e.g., R01). For fiscal year 2004, the funding success rates for NHLBI K08 and K23 applications were 27% and 28%, respectively. Eligibility requirements are the same as the other awards discussed (Table 7). The candidate's statement needs to include information about qualifications, commitment to an academic career, an actual need for further training, how the award will contribute to short- and long-term career goals, and a clear commitment of a minimum of 75% of time to the proposed research. The application also must include a detailed career development plan that takes you from the end of your clinical training to emerging as an independent investigator at the end of five years. The research plan is a formulaic one that all good science follows and the NIH asks for in their applications forms—specifically the hypothesis, specific aims, background, significance, preliminary studies, and the research design. Clearly, the research plan has to be appropriate for you and the stage of your career.

Again, picking a mentor is very important. The K08 and K23 applications are judged on all the aforementioned criteria, but the mentor may be the most important. The mentor has to state his or her willingness to protect your commitment of 75% of your time to your research program.

The K23 is identical to the K08, except that the K23 is for doctorate-prepared individuals who are going to do patient-oriented research. This is the kind of research that requires you as the principal investigator to interact with living, breathing, conscious patients. What kind of research would this entail? If you are interested in outcomes research

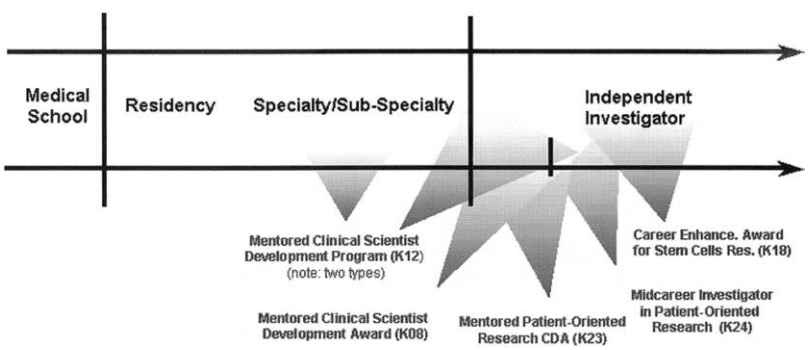

Figure 2. Career development awards (K awards) for individuals with a health professional doctorate. Note: Individuals with clinical doctorates may also be eligibl e for awards shown for individuals with research doctorates. The following awards are not shown: Academic Career Award (K07); Mentored Quantitative Research Career Development Award (K25); and Midcareer Investigator Award in Mouse Pathobiology Research (K26). Source: NIH website, http://www.nih.gov.

Table 7. Mentored Clinical Scientist Development Award (K08) and Mentored Patient-Oriented Research Career Development Award (K23)

Eligibility requirements
- Citizens or non-citizen nationals of the U.S.
- Permanent residents (Alien Registration Receipt Card I-551)
- Individuals on temporary or student visas are *not* eligible
- Clinical doctoral level degree: MD, DO, some PhDs (e.g., nursing, rehabilitation, audiology, clinical psychology, and so on)
- Completion of clinical training (both specialty and subspecialty) at time of award activation
- *Ineligible*: current and former PIs on NIH R01, FIRST awards (R29), comparable career development awards (K01, K07, K23, and so on), sub-projects of PPG or SCOR grants

Candidate: candidate's statement
- Qualifications (background)
- K08: commitment to a career in biomedical research (career goals and objectives)
  K23: commitment to a career in patient-oriented research (career goals and objectives)
- Need for further training
- How the award will contribute to the immediate and long-term career objectives
- Clear commitment of 75% of time to proposed research

Career development plan
- Likelihood that it will contribute substantially to the scientific development of the candidate
- Appropriateness of the content and duration of the proposed didactic and research phases of the award
- Consistency with the candidate's career goals and prior research experience
- Quality of the proposed training in the responsible conduct of research
- For individuals with limited or no prior research experience, the didactic component, proposed during the first year or two, must be fully integrated into the training program and justified based on their needs
- Interactions with an internal/external advisory committee

Research plan
- Specific aims
- Background and significance
- Preliminary studies
- Research design
  - Scientific soundness
  - Feasibility
  - Potential to achieve the goal of the award
- Appropriateness of the project for the candidate at his/her stage of development and as a vehicle to acquire research skills necessary for independence
- Inclusion of plans for the protection of animal and/or human subjects.

Mentor
- Research qualifications in the area of the project
- Extent and quality of his/her proposed role in guiding and advising the applicant
- Previous experience in training researchers
- History of research productivity and support
- Provisions for internal/external advisory committee
- Protection of at least 75% of candidate's time to proposed research

(For more than one mentor, the qualifications, role, and commitment of each must be discussed)

Environment and institutional commitment
- Specifics of the types of facilities, resources, and training opportunities available to the candidate
- A minimum of 75% of full-time effort will be protected for the program

Letters of reference (3)

Application receipt dates
- February 1st, June 1st, October 1st

Salary
- Institute specific
- Generally = ~$75,000 (legislated maximum salary 2005 = $180,100)

Research development support
- Institute specific
- K08: up to $25,000/year; K23: up to $50,000/year

Facilities and administrative costs
- 8%

on heart failure patients and you will be interacting with patients in your heart failure clinic, this is for you. If you are mining an existing database for new and unique markers for cardiovascular disease, then a K23 award is not appropriate.

A misconception is that the K23 award cannot have hardcore basic science components. If you have three or four aims, one of which has to be achieved working with patients, then you can be translating observations that you are making in

your first three aims on mice or zebra fish; it qualifies for a K23 as long as there is a human study component.

The success rate on K23 award application acceptance is very close to the K08 awards at the NHLBI and several other institutes. Once again, the application requires exactly the same information as the K08. And remember, if you are not successful the first time, the success rate on resubmissions for many of these is even better.

Question and Answer

Question: How mobile are awards like a K08 or K23? If they are mentor-dependent, how do you travel with them?
Dr. Balke: These awards are very mobile. All you have to do is demonstrate to the National Institutes of Health (NIH) administrative staff that you're going to a mentor and an environment at least as good as you were in your original institution. This happens all the time. It does not have to get re-reviewed or go back to a study section. Obviously you can't move one of these awards into a private practice situation and have it continue to support your salary, but otherwise they are very mobile awards.
Question: Many of the awards you mentioned are more to give you support for your salary. Are there other grants or awards that pay for your research, for example, to enroll patients or to do a statistical analysis or other direct research purposes?
Dr. Balke: Let me explain how the actual dollar amount works. You are absolutely correct that the majority of the monies are for salary protection. Depending on the institute and the award, you may request as much as $50,000 per year for supplies and research support. Because these are mentored awards, the NIH expects, actually demands, that the mentor have enough resources to help you get your work done. If you have a clinical trial as part of your project, obviously $50,000 is not going to fund a clinical trial of any worthiness. But it is your mentor's resources and the institutional resources that will provide that. That is why the mentor is so important and the criteria of having a mentor being funded in a peer-reviewed setting and being productive is so essential. If you have a mentor who does not have a grant, you will not get a K23 or a K08.
Question: Can the NIH loan repayment program be combined with some of these other grants, or are they mutually exclusive?
Dr. Balke: They are absolutely independent of one another and you can have both, so you should apply for both. Also, you can qualify for the loan repayment program without any of these other awards, too.
Question: What do they mean when the requirements talk about covering 75% of your time? Is that based on a 40-h work week, or does it mean three-quarters of the time that you spend working in research?
Dr. Balke: The answer from the NIH is a little murky on that, but generally, when institutions with K awards have been investigated by the Office of the Inspector General, the interpretation of that rule is based on 75% of your total effort. So, if you are working 80 h a week, it is 75% of 80 h. If you are working 40 h a week, it is 75% of 40 h. The NIH is not going to play games with these time percentages. For example, you cannot claim 75% of a 40-h work week for research and then have your department chairman make you work every weekend in the clinic to make up for this protected time. It does not work that way, which is a good thing for you as you are trying to establish your career.
Question: If you are in the second half of your training, doing research, and thinking about applying for an award, would you recommend going for the National Research Service Award (NRSA) or for a K08 or K23?
Dr. Balke: I would apply for an NRSA, even if it is only for a year. You are a principal investigator on an NRSA. Then when you go in for your K23 or K08 you have already started to develop a reputation and a track record for being a funded investigator, and that looks great on your application. You will use a lot of the things that you learn in the NRSA for the K08 and the K23. I would suggest you not waste an opportunity to get a score on the board, even if it is only a field goal, which the NRSA might be.
Question: Some mentors say just go directly for the K08 or K23; do not waste time with an NRSA.
Dr. Balke: It depends on your institute and what your discipline is, but you cannot have a K08 or K23 activated unless you are a junior faculty member. So, if you are in your third of four years of fellowship, I would apply for an NRSA for my fourth year of fellowship. This time next year I would be preparing my K08 or K23.
Dr. Fuster: Say I am finishing the training program and I heard all this talk about productivity, productivity, productivity, and I have two choices. One is to write the proposal for an NIH grant; the other option is to begin working on a research project because I am convinced I can write a paper faster than going through all that. I think getting funded at that stage is the most important goal. Would you interpret what productivity means at different stages of careers?
Dr. Balke: For an example, let us assume you are in your third year of fellowship and you have got only X amount of hours in the day. Do you apply for an NRSA or do you finish a paper? I do not see them as mutually exclusive. An NRSA is not that difficult of a grant. It is shorter, and much of what you do to produce a paper will go into your NRSA anyway. If you are doing a paper, those are your preliminary data. When you write a paper, if you do it well, the paper is addressing a hypothesis; that hypothesis is going to be part of your grant. I do not necessarily see it as an either/or situation.

When applying for the K08s, K23s, or the R01 awards, your ability to compete increases with manuscript productivity. That is when you really want to start getting some traction with those applications. However, you can get a K08 and a K23 without a lot of publications. If you finish your fellowship with one really solid publication in a good journal, you have more than enough to launch a K08 or a

K23. I am chairman of the National Heart, Lung, and Blood Institute K23 study section. I have seen applications come in with one or two papers that are superb, from *JAMA*, *New England Journal of Medicine*, *Nature*, *Science*, *Journal of Clinical Investigation*, *Cell*, and so forth. One or two papers, four years worth of work, two years in the lab, and two years in the clinic, that is great. You see applications come in with 14 papers in cardiovascular niche journals, and they do not succeed. You have to try to strike the right balance.

Dr. Fuster: When you are ready for publication, before you do anything else, should you discuss with your mentor about the order of authorship?

Dr. Balke: Absolutely. This is hard for all of us. One of the sort of silent genes that select us for being in medicine is the fact that we do not really address issues, we kind of settle them as we go along. This is your career. This is your life. Grab it by the horns and do not be passive about it. Be polite, but do not be passive. Sit down with your mentor and say, "I really am interested in this project you are doing with T-wave alternans, for example. I know this is your project, but I am going to meet these patients, I am going to analyze the wave forms, I am going to do the statistics. Where is my name going to be listed on this paper?" And if you agree with wherever he or she puts you, that is great, but it is also all right if you want to be in a different position. Recognize that your mentor may say, "I started this project, there is this other more senior fellow who has been doing a lot of the work, so he or she will be first author, you will be second, and I will be last. But let us see how the project concludes. If, for some reason, the percent contribution changes, then we can always revisit this."

I have accepted and actually administered that kind of a position a number of times. It often ends up exactly the way it was originally described, but it can change later. The last thing you want to do is set up a situation where you put a very acrimonious wedge between you and your mentor because you had one idea in your mind, he or she had another, you did not talk about it, and then when the paper goes out the door, you have big disagreements. Life is too short and you do not need that kind of aggravation. So ask up front. Nobody is going to be offended if you do. Just be polite about it.

Dr. Fuster: Can you give a sense as to whether authorship order is important, or is it more important that you can transmit how you contributed to a paper?

Dr. Balke: At this stage in your career, it is paramount to contribute at a level that gets you author attribution anywhere in the author list. Once you are on the author list, then order has some importance. First author is the best, and if you can get that position, please try. Being first author means you are the person who really made the project happen. It is not necessarily your idea but you understood the idea, you did a lot of the work, you contributed intellectually and substantially to the completion of a project, and you are sort of the fulcrum that all the different pieces went through. The last author is usually the person whose laboratory or research program conceived the whole direction. If you cannot be first, be second. If you cannot be second, be third. Get as close as you can to the front of the line.

If you are a second- or third-year fellow and you are in the middle of a pack of 20 authors, it is still okay. It is a publication. But no matter where you are on the list, when you go for an interview or when you write your description of your grants, talk about it like it is your project. You have got to know it. You just cannot be along for the ride. If I am interviewing someone for a junior faculty position and I have a fourth-year fellow who has got a couple publications, maybe first author in a small journal article but fifth author in *Journal of Clinical Investigation*, if he can tell me the hypothesis and he gets excited about the work and tell me what he and the team did, I do not care if he is fifth or first author; at that point, it is all the same. He contributed; it is his or her work.

Dr. Fuster: Do you think it is right or wrong for a senior research member, the one who runs the area and has a lot of experience, to give someone else the opportunity to be last author?

Dr. Balke: I do not know that I would say it is right or wrong. It is a matter of personal style. At this stage in my career—I finished my training in 1991—I do what I can within the honest scope of the work to give the last spot and corresponding spot to junior faculty when I can. Here is a very specific example. We have a program looking at some of the molecular determinates of contractile dysfunction in heart failure and we are doing a number of animal models. This has been a long-standing research program that I developed when I was a post-doc and have continued ever since. But for the latest paper, the clinical fellow is actually the first author, the new junior faculty member is the last author, and I am the next to last as corresponding author. The next paper that we put out on this model in this group, new junior faculty members will be the last end-corresponding author, and I will be buried somewhere in the middle. It is fine by me. And it is not dishonest. One thing you cannot do is put people on the list or in positions if they have not contributed to the work. That dilutes the quality of the science and the whole process that we are all so completely vested in.

Dr. Fuster: I agree every contributor should be there and someone who is not a contributor should not be. I feel very positive about giving people the opportunity to be the last author. When we talk about the importance of altruism, this is how it makes things go. It is to create incentive, and I feel very strongly about what you said.

Dr. Balke: Let me add that if you can find mentors who say they will use their seniority and clout to help get the first several papers that result from the work you do together into the best journals and then will voluntarily remove their names from later publications to help you develop your own reputation as an emerging independent scientist, that is the kind of mentor you want to wrap your arms around and

never let go. That is a generosity you rarely see, but it is what you need.

In our study section, I occasionally see situations where mentors are secure enough that they actually make explicit in their support statements for the candidate these kinds of generous offers. If you can pair yourself with someone like that, it will be one of the best opportunities in your entire career. Even if you do not find a mentor like this, put this in the back of your mind and when you mentor, which will not be many years from now, you should do the same thing. It is not a question of whether you have 2 or 300 publications in your curriculum vitae, it is a question of the quality of the work.

III. BRIDGING FUNDING OPPORTUNITIES FOR YOUNG INVESTIGATORS

Robert O. Bonow, MD, FACC (Northwestern University Feinberg School of Medicine, Division of Cardiology, Northwestern Memorial Hospital, Chicago, Illinois)

The number of young investigators under the age 35 getting their first National Institutes of Health (NIH) grants has declined from 23% in 1980 to about 4% in 2001 (4). The difference is not made up by the next level faculty, those age 36 to 45 years, where there has been no growth in numbers. We have lost a generation of investigators; the same investigators who could now be serving as mentors for the next generation. This is making it tough for young investigators to find good mentors, although it certainly can be done. This drop-off in young NIH grantees explains why many of us consider MD investigators an "endangered species."

This is especially a concern, given that during the period from 1990 to 2000 many more PhDs than MDs applied for NIH grant funding, although the overall level of funding stayed somewhat the same during this period (Fig. 3). Importantly, MDs and PhDs have a similar chance of successfully getting funded. We need to get young MDs enthused about getting funded and see to it that they get the job done.

Also of concern are a number of other issues that impact an MD's life in academia. For instance, how does this discrepancy between PhD and MD researchers translate into whether they get the next grant? In terms of investigator-initiated individual grants (R01s), nearly three times as many PhDs than MDs are first-time awardees. When the award comes up for renewal, more than two-thirds of PhDs try to get their grant renewed, but only about 47% of MDs seek renewal. As for the percentage who are successful getting their award renewed, only 17% of first-time awards for MDs get renewed, which accounts for only 70 of 405 first-time awards granted in 1996. That compares to a 33% renewal success rate for PhD applicants. So, we are not only losing MDs who might become grant recipients the first time around, but then they are dropping out after the initial award for a lot of competitive reasons.

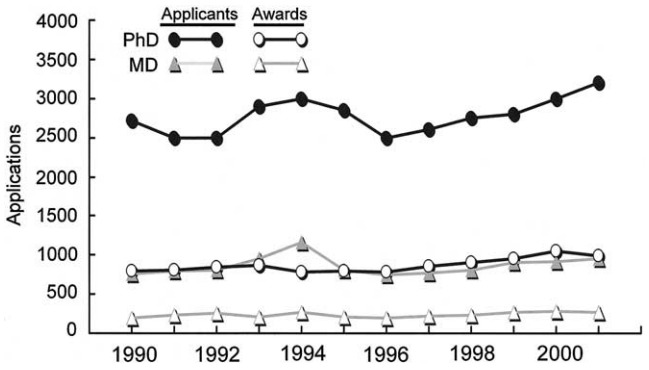

Figure 3. NIH funding: first-time applicants and awards 1990 to 2000. From Nathan DG, Wilson JD. N Engl J Med 2003;349:1860–5.

Part of this is related to the fact that the transition from fellow to faculty is one of the most difficult hurdles on the path to a career as a clinical investigator. What can be done to make this transition a little easier? At the NIH, there are important transition awards for junior faculty members as well as those in the last stages of fellowship, as discussed by Dr. Balke.

There are other institutions offering support as well, including the American College of Cardiology (ACC), the American Heart Association (AHA), and the Department of Veterans Affairs (VA). Take these opportunities seriously. If you go to the AHA Scientific Sessions, for example, there is a Saturday afternoon session in which you can get survival skills necessary for early career development. You can have one-on-one discussions with successful scientists as well.

Transition awards—AHA. While funding from the AHA is only about 5% of the total funding of the NHLBI, the AHA focuses most of its research funding on young investigators. The AHA strategic goal for research is to identify opportunities and implement programs to increase the number of beginning investigators; specifically, those with no more than four years since their first full-time faculty or staff appointment.

There is a portfolio of possible grants from the AHA that differ among the AHA affiliates and the organization's national level of programs. This discussion will focus on the Scientist Development Grant and the Fellow-to-Faculty Transition Award. The Scientist Development Grant supports highly promising beginning scientists in their progress towards independence (Table 8). For this grant, applicants should be a faculty/staff member or a fellow who is about to become a faculty member. Applicants must be initiating independent research careers at the early faculty level, usually at the rank of instructor or assistant professor (or equivalents). Applicants can be writing this grant and getting the award while making the transition.

The Scientist Development Grant applies up to $30,000 per year towards salary plus 10% for indirect costs, as well as $35,000 per year for project support. If grant recipients have other means of funding their salary, much more of the grant money may be applied to project support. For example, if a

Table 8. AHA National Scientist Development Grant

Objective
- To encourage and adequately fund research projects that bridge the gap between completion of research training and readiness for successful competition as an independent investigator.

Eligibility
- MD, PhD, DO, DVM, or equivalent doctoral degree who is a faculty/staff member initiating independent research careers, usually at the rank of instructor or assistant professor (or equivalent).

Citizenship
- U.S. citizen
  - Permanent resident
  - Foreign national holding HI, HIB, TC, TN, or O1 status

Budget/annual award amount
- Principal investigator salary/fringe: up to $24,091/yr
  - Project support: at least $35,000 per year (all of award may be budgeted for project support and 10% indirect costs if PI salary/fringe are not requested)
  - Indirect costs: not to exceed 10% ($5,909)
  - Maximum annual amount: $65,000

Online
- http://www.americanheart.org/presenter.jhtml?identifier=3004142

Source: additional details provided from http://www.americanheart.org/presenter.jhtml?identifier=3004142.

grant recipient is joining a faculty and will be doing echocardiograms one day a week, that may generate enough to cover the recipient's salary, leaving more of the grant money for project support.

The intent of the AHA Fellow-to-Faculty Transition Award is to provide a supportive mentored experience during this transition period (Table 9). This is not funded heavily at the local affiliate level, but has a high success rate if you apply for this at the national level. Applications can be made to either the affiliate or national grant sections, and sometimes it may be appropriate to apply to both. With this award, one may obtain research support during one's fellowship and carry the remainder into the early faculty years.

It is important to indicate participation in a strongly mentored research program, which is very similar to the NIH K award application process. Therefore, applicants will be judged strongly not only by their own interests and science, but also by the scientific track record of their mentors.

Fellows can receive the award for work at one institution and then carry it to another institution where they join the faculty.

Other AHA programs for beginning investigators include the Beginning Grant-in-Aid and the Established Investigator Grant. The Beginning Grant-in-Aid program is designed to promote independent status to promising beginning scientists up to and including the faculty level of assistant professor or equivalent. This award is less frequently funded within the AHA portfolio because there is more support going to the Scientist Development Grant. However, in some of the AHA affiliates there may still be available funding for Grant-in-Aid. When looking for the programs offered by AHA affiliates, see what is being funded in any given cycle or in previous cycles to determine those awards that may be applicable to your situation, but understand that the Scientist Development Grants are going to be much more attractive, and that is where the AHA wants to put the money.

The Established Investigator Grant is for someone at the next career level beyond fellowships. This award is for individuals who have already established themselves as independent investigators and is meant to support the career development by funding innovative projects not funded elsewhere. The grants usually are given to investigators four to nine years after their first faculty or staff appointment. This is the kind of prestigious grant that should be a goal for serious young investigators.

Beginning investigators should be applying for grants at the NIH K award level as well as for the Scientist Development Grants. It is not possible to get funded from both arms, but it's wise to apply for both; if an applicant gets rejected by one program, they may get accepted for the other. The same thing is true for the Established Investigator Grant, as investigators move up the NHLBI grant program ladder as their career advances.

For the year 2004, exactly 60% of AHA research funding went to applicants at the level of assistant professors, fellows, and instructors. Other career guidance information is available from the AHA, including mentoring information and the AHA Mentoring Handbook (5), at the organization's web site, www.americanheart.org/research. Becoming a member of the AHA gives you access to myamericanheart.org, which provides

Table 9. AHA Fellow-to-Faculty Transition Award

Objective
- To provide funding to physician scientists during critical period of career development spanning completion of research training through early years of first faculty/staff position.
- To provide a supportive mentored experience during this transition period.

Eligibility
- MD, MD/PhD, DO, or equivalent doctoral degree who needs additional research training under sponsor/mentor supervision before independent research.

Citizenship
- U.S. citizen
  - Permanent resident
  - Foreign national holding HI, HIB, TC, TN, or O1 status

Award amount
- Training portion
  Up to $65,000/yr
  Provides for no indirect costs
- First faculty/staff appointment
  Up to $132,000/yr
  Includes 10% indirect costs

Total amount
- 5-year maximum @ $593,000
- Duration, 5 years, with annual review

Online
- http://www.americanheart.org/presenter.jhtml?identifier=2230

Source: additional details provided from http://www.americanheart.org/presenter.jhtml?identifier=2230.

Table 10. ACCF/Merck Research Fellowships in Cardiovascular Disease and the Metabolic Syndrome

Objective
- To support research addressing diabetes or the metabolic syndrome as they pertain to cardiovascular disease

Eligibility
- Anyone currently in a recognized, accredited adult cardiology fellowship training program
  - Preference given to individuals with no more than 2 years of prior full-time research experience.
  - Preference given to clinical research training and experience directly involving patients or human subjects.

Award amount
- $60,000
  - 1-year research fellowship (four awarded annually)
  - Full-time research commitment

Online
- http://www.acc.org/about/award/awardopps.htm#metabolic

even more specific career information as well as more specific ways to obtain grant support from the AHA.

Transition awards—ACCF. The American College of Cardiology Foundation (ACCF) is a very attractive source of information and funding for fellows. There are fewer grants available, but they are quite prestigious. The ACCF/Merck Research Fellowship awards are for one-year research fellowships with preference given to individuals with no more than two years of full-time research experience (Table 10). The new focus of this award this year is cardiovascular disease and the metabolic syndrome.

The ACCF Career Development Awards (Table 11) are for junior faculty. There are separate awards for investigators involved in research related to heart disease prevention and hypertension/peripheral vascular disease. Applications may be made by fellows as long as they have a faculty appointment for the next year.

For those with imaging interests, there is a new award available: the ACCF/General Electric Healthcare Award for Cardiovascular Imaging (Table 12). The intent of this award is to support investigators looking for innovative new strategies for imaging and/or new imaging agents.

The ACC also offers the ACCF/Pfizer Career Development Award in Clinical or Preventive Cardiovascular Medicine (Table 13), which is a clinical research award. Each medical school can recommend only one candidate. New in 2005 is the ACCF/Guidant Foundation Fellowship and Career Development Award in Women's Cardiovascular Health (Table 14) to encourage research in cardiovascular disease in women. More information about various awards is available at the ACC website, specifically at www.acc.org/about/award/awardopps.htm.

Table 11. ACCF Career Development Awards

ACCF/Harry B. Graf Award for Heart Disease Prevention
ACCF/William F. Keating Award for Hypertension and Peripheral Vascular Disease

Objective
- To foster the early research career development of junior cardiovascular faculty in research areas specific to each award

Eligibility
- No more than 5 years out of training
  - Academic rank of instructor or assistant professor
  - ACC member

Award amount
- $65,000, solely for salary support
  - 1-year research award
  - Full-time research commitment

Online
- http://www.acc.org/about/award/awardopps.htm#

Table 12. ACCF/GE Healthcare Cardiovascular Career Development Awards in Cardiovascular Imaging

Objective
- To foster the early research career development of junior cardiovascular faculty in the area of imaging technologies and targeted imaging agents.

Eligibility
- No more than 5 years out of training
  - Academic rank of instructor or assistant professor
  - ACC member

Award amount
- $65,000/year per award, solely for salary support
  - 2 two-year research awards
  - Full-time research commitment

Online
- http://www.acc.org/about/award/awardopps.htm#ge

Transition awards—NIH, VA, and Foundations. In addition to the many extramural K awards discussed by Dr. Balke, investigators who are early in their training might consider going to the NIH, working in a laboratory with world-class people. The NIH K22 Career Transition Award is an important research fellowship within the NIH in the intramural branch, which is an intensive research environment—effectively a huge clinical research center with 100% research time. As a research fellow, you can take this K22 transition grant with you when you transition out of the NIH.

This K22 award requires an intramural phase at the NIH, which includes direct costs of up to $150,000 per year including salary, followed by an extramural phase during which the award continues, provided there is an extramural faculty appointment that is on a tenure track. The extramural phase requires at least 75% research time for two years

Table 13. ACCF/Pfizer Career Development Award in Clinical or Preventive Cardiovascular Medicine

Objective
- To provide training opportunities for physician-scientists to pursue cardiovascular research in an academic setting.

Eligibility
- MD or DO degree
  - Instructor or assistant professor not more than five years out of training
  - ACC member

Award amount
- $65,000/year
  - 3-year research award (up to two awarded annually)

Online
- http://www.acc.org/about/award/awardopps.htm#pfizer

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October 4, 2005:5A–72A

Table 14. ACCF/Guidant Foundation Fellowship and Career Development Award in Women's Cardiovascular Health

Objective
- To encourage clinical research that will broaden scientific knowledge related to the mechanisms or treatment of cardiovascular disease in women

One Fellowship and One Career Development Award
- Fellowship
  - Current fellow or within one year of training
  - Mentor with recognized experience in treatment or research in cardiovascular disease in women
- Career Development
  - Instructor or assistant professor with no more than five years out of training

Award amount
- Each amount: $65,000/year
- Two-year research award

Online
- http://www.acc.org/about/award/awardopps.htm#guidant

and provides up to $150,000 per year in direct costs including salary plus fringe benefits.

The VA also has Clinical Research Career Development Awards (www.va.gov/resdev), but they are only applicable for investigators on staff with salary support at a VA hospital on site. The intent is to foster research careers of clinical scientists who are not yet fully independent but will soon become independent clinical investigators. The VA awards share similarities with the NIH K awards and the AHA Scientist Development Grants; specifically, applicants are not yet fully independent, and they must have a strong mentor relationship. The VA awards provide three years of support, including salary and supplemental research support for a fully trained clinician scientist who is entering or has recently entered a career in clinical research.

Finally, there are many foundations interested in supporting young careers. These foundation transition awards come from foundations such as the Schweppe Foundation, Doris Duke Foundation, Robert Wood Johnson Foundation, and the GlaxoSmithKline Research and Education Foundation for Cardiovascular Disease. There are many additional local awards, and they can be found in the cities where your institutions reside. This is where a mentor can be quite helpful, because many mentors know about these awards and have used them successfully.

A successful transition requires dedication, focus, and mentorship. Importantly, you should have fun and enjoy this part of your career. Many of us are overachievers—we like instant gratification and do not take bad news easily. On the other hand, a successful research career is like a rollercoaster ride. Every young investigator will face times of rejection. You have to have a thick skin. You have to have persistence. Yet, it is a very invigorating career, and it can be enjoyable. You get to meet interesting people, and you are given the opportunity to teach the next generation of interesting people. It is a very rewarding experience.

IV. PANEL DISCUSSION: OPPORTUNITIES FOR YOUNG INVESTIGATORS

Valentin Fuster, MD, PhD, FACC (Zena and Michael A. Wiener Cardiovascular Institute and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center, New York, New York)

Robert O. Bonow, MD, FACC (Northwestern University Feinberg-School of Medicine, Division of Cardiology, Northwestern Memorial Hospital, Chicago, Illinois)

Augustus O. Grant, MB, ChB, PhD, FACC (Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, North Carolina)

Dr. Fuster: About 4% of young investigators are funded by NIH grants today in comparison with 28% in 1980. I would like to ask, why is this happening? Is it because cardiology offers other funding opportunities? Or is it getting tougher? One would think that it should not be getting tougher because all of us have been presenting information here suggesting that there are more opportunities than ever. So, what is actually going on here, Bob?

Dr. Bonow: I am not sure I have the answer. You could argue that the 4% figure for funding is a little misleading. Maybe the grant is going to an older investigator, and younger people are being supported through that grant.

However, I do not completely buy that explanation because if you look at that intermediate group of researchers 35 to 45 years of age, that group's funding is not expanding either. I am concerned that we are kind of an endangered species with fewer and fewer people going into research. By the way, that graph I showed was not just cardiovascular disease research funding; that was funding across the board. It may be worse in cardiovascular disease research, possibly because clinical cardiology is so exciting. When you start saving lives at 3:00 in the morning with a balloon catheter, that can be habit-forming; who has time for research?

Training programs are supposed to be training clinicians as well as scientists and future academic leaders. In any cardiology training program, we accept the fact that a number of participants will ultimately go into clinical practice. As a profession, however, we must provide not only the tools but also an environment that encourages young people and attracts them to research.

The reason we have this meeting is to give you the opportunity to discuss with all of us your aspirations and the difficulties or hurdles you face. I do not have the answer. All I know is that the data tend to speak for themselves and, of course, many others have been raising alarms regarding funding for a number of years. As a result of those alarms, many of the National Institutes of Health (NIH) career development awards came to fruition, and the K awards have been very successful. So, we may see a turnaround in this as we update that graph over the next 10 years.

Right now, the K award applicants get funded at a very high level. If you apply for a K award with a good mentor and a good project, you have got almost a 40% chance of getting funded, which is great. From my perspective, the problem is going to come in the success of moving K award recipients into R01 grants, which is the original and historically oldest grant mechanism used by NIH. Going from a K to an R01 grant moves you from the mentored experience to the independent experience. That is an important step because they are not funded at the same level.

Also, there is the NIH budget itself, which is going up each year, but the budget has gone from increasing 15% per year in the last five years to just 3% this year, with a lot of that increase going to bioterrorism, not cardiovascular disease. So, the ability to take all those K award recipients and advance them into R01s is going to be tricky.

I have a question for Dr. Fuster: While the team approach is a great concept, how do you reward the team player in the current academic environment? The person with a grant tends to get all the credit at the university, in terms of promotion and so forth, so how does the dean recognize a good team player? Certainly you contributed to this grant, but you are not the recipient or principal investigator (PI) on it. A lot of medical institutions are struggling with that issue. We all agree there is a need for team-based research and building new research teams.

Dr. Fuster: In my view, the NIH is stuck in the PI concept, and this is a mistake. As we move towards the future, we must identify young people and provide the resources and incentives necessary for these people to be recognized. Unless this is done, it is going to be a huge problem.

Question: My question relates to clinical work versus research. Many of us love clinical work but are also drawn by research. As fellows, we are trying to find a way to combine them and be happy with both worlds. Is that truly possible?

Dr. Grant: I would say, it is. If I have conveyed the idea of a dichotomy, I would like to correct that. On the one side, there is someone like Dr. Vatner who spoke with you earlier about dedicating yourself to basic cardiovascular research. As for myself, I have been on the Duke faculty for 25 years, and I continue to see patients while I run an NIH R01-funded laboratory. So it is possible to do both.

The question is: how do you divide your time? I commit a majority of my time to basic research, but it is certainly possible to still maintain my clinical contact. After all, that is why we became physicians in the first place. If you are trying to decide your commitment in terms of effort and time, then my message is this: if your maximum commitment is to basic research or to clinical patient care, there are differences in lifestyle involved. But both are rewarding.

Dr. Bonow: Also, it depends on the kind of research you are talking about pursuing. If it is a highly competitive area of basic investigation, that can be difficult, which is why we talked about focus. That scenario would require an 80% minimum commitment by you in order to be competitive with the PhDs who do this 100% of the time.

Yet even if you are doing basic investigation, it is great to have a clinical presence. It makes you more aware of where your research should be going, the real world it is going to be applied in, and why the research is important. Also, having that clinical presence helps you keep from getting off track into some irrelevant area, and it allows younger trainees to see you as a real doctor, and perhaps it will help you draw them into your laboratory. And there is another bonus, too: reserving some time for clinical work maintains the reason why you went to medical school in the first place, and that is the patient experience.

All of that applies to basic laboratory research. If your research is more clinically based, it may be quite easy for you to be in a cath lab involved in research of vascular function, for example, or myocardial infarction or medical devices. In the cath lab, you are dealing with those cases every day, and half of what you do clinically may be adding to your research database.

So, I agree with Augustus: certainly you can combine both clinical and research work, but when you do that your focus becomes really critical, and you have to watch your time on the clinical side.

Dr. Fuster: I would like to add to what Bob said. I have combined clinical research and clinical practice all my life. It is hard, although it can be very enjoyable. What you must remember is that you are competing when you apply for grants. It is impossible to do basic science today and be a great clinician because the competition is so much greater. But it is possible to take the clinical investigation track and be a translational researcher working with basic investigators and enjoying what you are doing while still getting grants. However, to make it work you have to be methodical with an organized pattern in your life; it has to be very strict.

Dr. Grant: This comes back to the issue of focus again. If you are interested in vascular biology or some other particular area, an ideal research career would be to select a group of patients who have a related problem and then work towards gaining focused clinical experience directly related to your research. With a career built around that sort of paradigm, you can be extraordinarily successful.

Question: Dr. Bonow, you were speaking of the American Heart Association (AHA) Fellow-to-Faculty Transition Award, and there are the K08 and the K23 Transition Awards as well. It seems as though it would be difficult to be part of a mentored program if you are going to leave the institution where you are doing fellowship and go to another institution. To me—unless I am not understanding the award—that seems like a limitation. How do you identify a mentor at an institution where you have not been hired yet in order to obtain one of these awards?

Dr. Bonow: It is tricky, but it is possible. It requires homework and long-distance mentoring, just like we talked before about the ability to reach out and identify potential mentors. As part of the recruitment process, you could be doing that. As you are selecting one place over another, due

diligence is your responsibility to identify those individuals who will mentor you.

I should add that, compared to the NIH awards you mentioned, the AHA award is a little easier to transfer. You can pick that up and move with it if you need to. In doing so, however, you have got to be certain that there is a mentor on the other end of your move because there will be required review of your progress. If your progress was great as a fellow but it starts to slip as a faculty member because you moved, that is not good. So, if you are considering a move, you have got to look very carefully at the mentorship on the other side.

Question: I hear that sometimes, even though you are working with a good mentor, it is better to move to a different institution as faculty to get a better opportunity and more experience. Can you keep the same mentor and do this long distance, or is it better to just stay in the institution where you are a fellow, finish your work, and then move?

Dr. Bonow: It depends on your work. It may work if you are dealing with a database and outcomes research. If it is bench research, it will be virtually impossible unless you are just finishing up some data analysis and writing it up in the transition period.

There is no problem in staying. This comes up all the time as we are talking with fellows about getting faculty positions: is it better to go someplace else where you might get a better deal? Also, if you move, you are coming in to your new position as an accepted senior person as opposed to somebody who has been a fellow and is now just moving into faculty. It is very individual and based upon you, the institution, and your track record there. Independent of that personal feeling of whether you should stay or go, the key issue is what will a move do to your research career? Is it going to suffer because you are moving?

The question often comes up: when is the right time to leave and move? Frankly, it comes up not only as a fellow but throughout the rest of your life. All of us have had opportunities almost every year to change our stripes and go someplace else. I bet Augustus has had offers this year and Valentin has, and I have too. At some stage, you decide this might be the right thing to do. But if you are productive and successful, the offers only get better. Therefore, if you are doing well where you are, you might join the faculty at that institution for a couple more years, get a few more grants, become independent, and then when you have the R01 you might want to leave.

Dr. Grant: In a lot of ways, this is truly a personal decision. And the decision should turn around specific arguments, for example: am I really at the stage of my career where I can truly be independent? Do I have the skills that I need to stand on my own feet? Am I prepared to write—or better still, have been successful at writing—my first grant? Can I comfortably sit down with my data and prepare a completed manuscript? If you feel that all the pieces are in place and you are truly comfortable with where you are in your career, then I say the decision can go either way.

If you can identify deficiencies in your skills at any level, and you are in an environment in which those deficiencies can be corrected, then surely the answer is to stay longer and not move. It is a very personal decision, and you must reevaluate it from time to time. There is no timetable or any rules to tell you exactly when that transition is appropriate.

Question: I have a question about the Fellow-to-Faculty Transition Award. Do you have to be actively engaged as a fellow at the time of the award?

Dr. Bonow: Yes, and because of the award you may decide to extend your fellowship. There is nothing wrong with getting a couple of extra years of fellowship training if you are in an environment where you are really protected. As soon as you join the faculty, your protection becomes a real issue; even when you have 75% protected time, you will have people biting at your heels to spend a little more time seeing patients, doing other things. That is where you need a mentor to protect your time and stand behind your grant. If your fellowship is ending, then you would be eligible for the Career Development Awards, which are specifically for junior faculty.

Question: Do you think medical schools or universities could do more to assist in this transition into research, which seems to be the hard part? I am talking about making it easier in terms of support, because a lot of grants require the institution to make a commitment that could cost them $40,000 a year. That might be a problem in some institutions that do not have a lot of resources.

Dr. Bonow: It is true for NIH K awards, too, because they do not really support your salary. From the institution's point of view, K awards are great and yet every time we get one, we swallow hard because now we have got to find a way to support this person when 80% of their time is protected for research. Some medical schools are stepping up to do this better than others, and this is an important consideration as you are looking for faculty positions. What is the school's climate right now in terms of the environment and support for young people? If you get a K award, will you be protected? Will you be supported? Those are important questions to be asking.

Question: This question is about doing basic research and trying to learn some clinical research skills at the same time. It is hard to get protected time, but if you are doing some culture studies you may need three to six months of protected time. My concern is if a patient comes in maybe only once a year, will I be permitted to go and enroll that patient for my clinical research? That is part of the problem when you are a fellow.

Dr. Grant: That is a very good question, but you really need to decide your top priority. You cannot develop a meaningful career in biomedical research without a strong and almost total commitment to it. In our institution's fellowship program, if you choose either basic or clinical research, on the clinical side it requires a minimum commitment of one year. On the basic research side, most people who do laboratory research in our institution are going to ask you to

spend two years. Why the difference in the time you are being asked to commit? The complexities of basic biomedical research now are such that if you have never done it before, you cannot walk away with a meaningful experience without dedicating at least two years to it.

The idea that when there is a week or two available you should just go into the laboratory and get something done is not a serious proposition at all. I have had people in my lab who have not been totally committed in terms of their research time. They have got an experiment set up, but this person is really a pediatric cardiologist and not a researcher; someone comes into the clinic with an interesting congenital abnormality, they drop the test tubes, and run to do the catheterization. In my opinion, you cannot double up like that on a repeated basis and obtain a meaningful research experience. Like with many things in life, you have got to make a choice.

Dr. Bonow: Mike Mendelsohn showed a slide that said if you are learning bench research, you need at least two years in the laboratory if you are already experienced or three years if you have never really done it before to get up to speed. For you, it may be that you need to get the clinical training because you still want to be a card-carrying pediatric cardiologist, which is good. Then the issue becomes: what is the support system in your institution to give you an extra year or two of training?

Dr. Grant has noted that Duke University has such a system. We have kind of a system in place, too at Northwestern—anybody who wants a fourth year gets a fourth year. We hope they will get a grant for that fourth year, but if they do not, we will find a way to support them, whether they are doing basic or clinical research. Beyond that, if they are really committed, they will find a way to do the fifth year.

This is a discussion you have to have with your program director. If you cannot do it at your institution, perhaps you need to go get the clinical training you need and start looking now for that mentoring experience someplace else where you could be supported if you move. Obviously, if you can get a grant, that is great, but it would be good during your training period to have some protected time as well.

Dr. Fuster: This question is very important because it brings into discussion the issue of your own commitment. As you start seeing all the barriers and difficulties you face, you have to ask yourself if you are really committed to an investigational career or not. Most of us were not genetically made to do investigational work. I was at the Mayo Clinic, a fellow like many of you. I earned my degrees in cardiology in England, and when I came to the Mayo Clinic I started from zero. It was only after six or seven months that I found my way as a researcher, and it was only by working at night. You must commit to the fact that you want to be an investigator and then find a way to become an investigator—maybe by finding extra time to do research or whatever else it takes—but you need to have this commitment, otherwise it is going to be very difficult. Yes, the training program itself does not give you much time to do many other things, but if you are really passionate about research, then the time gets carved out for it somehow.

I am sure many of you are thinking that "What these guys are talking about is not for me." Yet, we are making a very attractive proposition to you today, as long as you are committed. You might say, "Well, I enjoy research in echocardiography. Forget about grants. I would just like to understand some basic issue in hypertrophic cardiomyopathy." Even with training programs being so tight today, you will find a way to do some work in hypertrophic cardiomyopathy and maybe write a paper or two with your colleagues. So, I do not think there are barriers if you really are committed and excited about something, and this is what we are trying to convey to you today. If you are not very excited, you probably should follow a different path.

Question: I have a very practical question regarding choosing a mentor in basic science research. Please comment about choosing somebody outside of cardiovascular research, maybe even in hematology, who is interested in biological questions with potential relevance to cardiology. Specifically, could you comment about institutional support, necessary grant applications, and ultimately finding jobs?

Dr. Bonow: This is one of the reasons why I believe divisions of cardiology should not be independent of departments of medicine because there are so many things in cardiology that interrelate, including immunology or hematology and inflammation, for example. Right now, we have a junior faculty member whose mentor is a bone physiologist because she is studying why valves calcify. It is all ossification and bone signaling, so non-cardiology collaboration should be allowed and fully supported. How are we going to succeed at team-based research unless we are reaching out to bring in different kinds of team members? Interdisciplinary or multidisciplinary research is encouraged in many places. I would like to think you would find within your department of medicine the support mechanisms necessary for this.

Dr. Grant: It is a good idea to think about skill set you want to acquire and then make your decisions independent of departmental barriers. I will cite a personal example for you: many years ago, I decided that I needed to learn more about molecular biology. I sat down and spoke with my department chair as to what laboratory I should go to, and we decided that the hematology lab was a great place.

That is because if you look in all systems, hematologists are one of the few groups of biomedical investigators who have ready access to the material being studied, namely blood. Some of the earliest and most fundamental work related to genetics and molecular biology was done in hematology laboratories. The heme-carrying proteins turned out to be very simple molecules, so this was a great place to go and acquire the initial skills I needed. Then I could return to my cardiology lab with the skills I learned in hematology. So, absolutely decide on what skills you need, and do not let departmental barriers stand in your way. Go wherever you need to learn those skills.

Dr. Fuster: This is critical. Forget about divisions, departments, or anything. We are in research, and today there are merging technologies across the board. So as to the question of who is your mentor, it does not necessarily have to be a cardiologist. You may require a mentor who is a hematologist, but I caution you that it is important that your mentor be in touch with the appropriate people in the cardiovascular division. It is critical that there is always a link between the divisions rather than a separation. That is important advice because I can give you examples of people who I suggested go to other divisions, but then the mentor absorbs that fellow. The fellow may be doing really well, but is somewhat being held hostage. When something like this happens, it is very important that there be communication with the appropriate people in your own fellowship program.

Question: My question is for those of us who short-tracked. Is there a feasible way to do preliminary experiments and generate data to satisfy early career grants while finishing clinical training but not having protected time when you have already done your three years in the lab? Or do you recommend applying for transitional funding, then trying to stay on as a fellow?

Dr. Bonow: It is always a question: how do you do the research versus the clinical training? So, you have already done your three years of research; now you are doing two years of clinical training. It would be great if you could have time to write the grant now for the work you want to do. The question is: what grant are you going to be applying for? Is this for a faculty Career Development Award as you look to transition into faculty, or are you going to try to extend your research training fellowship for a couple of years?

You may be able to get a couple more years of research training through a transitional grant. Based upon your three years of research, you should have the experience, mentorship, and preliminary data to write a very successful grant. Of course, you have to find time to do that in the middle of a clinical training period. We have also been wondering about this issue with the career development types of fellowships and the best approach for someone who is short-tracked. Perhaps we should schedule some research time into that last year, permitting somebody to get back into the laboratory again where they can have a little buffer time and be writing grants.

Dr. Grant: If you had a very successful three years and got two or more papers published, then I would strongly encourage you towards the end of your clinical rotation to start putting your ideas together into a grant proposal. The people who review grants, particularly at the AHA, understand the transitional situation, and the expectations are different. If, on the other hand, you feel you did OK during your three years but have a lot to learn, then you may want to get back to the lab first before writing that grant.

Dr. Bonow: But, Augustus, what would you recommend the target be in terms of the grant she is applying for? We are going to assume you are a very successful investigator: you have a successful three years, wrote a bunch of papers, and now what kind of grant should she be looking to move toward next?

Dr. Grant: Maybe the Scientist Development Grant.

Dr. Bonow: One of the Career Development Awards also would be good.

Question: When you are looking for a grant, how important are your preliminary data?

Dr. Grant: It depends on the nature of the grant that you are writing, but good preliminary data always help. It is reassuring to the people reviewing the grant that you understand the implications of what you are proposing and that you have some skills in problem-solving. On the other hand, there are grants for which preliminary data are not that crucial. To a certain extent, the grant depends on other variables too, such as the mentor you have identified, and the commitment of the institution and your mentor to you.

If you are going for a national award at the NIH level, preliminary data are definitely significant. However, in foundation grants, such as the Robert Wood Johnson Foundation or certain AHA grants, preliminary data are not that critical. It depends more on the environment you are going to work in and the commitment of the people around you to your success.

Dr. Fuster: I want to ask three young investigators if they have any questions or comments for us? Do you have any comments or anything you disagree with in terms of what has been said? Or is there something important, or any question that is left unanswered, from your own perspective?

Fellow 1: My experience with the postdoctoral fellowship grant is in an institution where a number of people write applications every year. Those who have preliminary data tend to get higher scores than the ones who do not, so preliminary data makes a difference. It probably makes a difference in your ability to write a good grant. If you worked in this field and have a little experience, it makes it easier to write.

Dr. Bonow: That is what Dr. Grant was saying: if you have preliminary data, it is always better than not having it. But the question is: should you even bother applying for this grant if you have no preliminary data? The answer is that there are some grants where the preliminary data really are not that important.

Fellow 1: But your score is going to be better if you do have preliminary data, so you are more likely to get funding.

Dr. Bonow: If you are competing against somebody down the street who has got preliminary data, then yes, it is going to be a tough competition for you.

Dr. Fuster: Veronica? Do you disagree with anything that has been said?

Fellow 2: I have not applied yet for a grant, so I do not know much about it. But I know that the more data you have, the better score you get, and the easier it is to get the grant. I have one question, though. Sometimes we get the

opportunity, as fellows, to mentor high school students. Is that good to do or not? How would you approach that?

Dr. Fuster: It is absolutely critical. We have a program—and I am sure the others can speak to similar programs—in which very young people at different stages have opportunities during the summer to come in to the medical school and you can tutor them. Some of the best experiences I ever had were to guide students before medical school into areas of research or interest or methodology and see their excitement. If you follow-up on these individuals, you tend to find that they go for academic careers. That is why I feel effort should be focused on that group of people very early because that is where the excitement really is, and sometimes they do not face some of the obstacles and problems you see later on.

Dr. Bonow: I agree; in fact, I wish we had more opportunities to expose young people to young investigators like you. That is because I am an old person, I am irrelevant to a high school student. But all of you are much closer to the action, and you can be the stimulus for the generation after you.

Dr. Grant: Every summer at our institution, we have high school students who spend four to six weeks on campus where they will be exposed to fellows in different areas. Some will get a chance to go up to the coronary care unit in the evenings and spend a few hours, just to see what you do—no hands-on experience, of course, but just to see what your life is like as a clinician. We will have perhaps 150 students on our campus during the summer.

If you run across any of them in similar situations, it is great to interact with them, and let them see the fun you are having. And I stress that point about having fun. About five years ago at Duke University, we did a survey to find out what had the greatest influence on fellows like you in regards to choosing a career in academic medicine. And this is perhaps a word of caution to the three of us sitting up here; the fellows decided that the most important thing was the happiness of the faculty around them. If it was not apparent that the faculty was really having fun and enjoying what they were doing, then the fellows decided that this career really was not for them. The lesson is that, if we do not reflect the fun that academic medicine really can be, then surely you look in from the outside and consider it unattractive. And let me reassure you: this can indeed be a fun thing to do.

Dr. Fuster: Augustus, this leads to a very important question about competitiveness. In general, one of the dilemmas for young faculty members is that they are struggling because there are so many demands clinically, and, at the same time, they are working in the research arena, and they have to survive. Then you find a young person who comes into the system and begins to notice the tension and stress. Please comment about how you view this.

Dr. Grant: It is a very important issue, and this issue of stress and tension is, in part, the reason I mentioned it. We do not convey nearly as often as we should the fact that what we do is fun. Yes, it is reasonable to be competitive, but you can be competitive in a very honest way and in a way that is meant to be a search for truth, but the goal is not to be better than anyone else. The more we all stress the positive in terms of those interactions, the better off both sides will be.

Dr. Bonow: For the three of us here and those like us who are out there doing what we do, we need to expose fellows to the research successes of our faculty. Fellows are caught up in the day-to-day clinical arena. They see negative things; they know all the dirty laundry long before I know about it. We need to expose them to the excitement that some of the faculty is having with other fellows, and the fact that other fellows are getting their papers in really good journals. At the same time, we need to expose fellows not only to the successes of their peers but also to the fun and excitement that can go with it. We have research conferences, and those are helpful, but getting fellows to come to our meetings is hard sometimes, so we try to mandate that fellows attend those meetings.

Fellow 3: I fully agree with the idea of getting people exposed early to research. My own exposure to the field of research occurred when I was a junior in high school. Through a program at Washington University in St. Louis I was exposed to a top-notch electrophysiology laboratory, and I made a decision at that time to be a researcher.

Dr. Fuster: We could summarize by saying that the opportunities are great in the research arena and certainly in clinical research, which we have not touched upon much in this conversation. You have to find out for yourself whether or not you really enjoy this kind of work. How will you know? Maybe you will wake up in the middle of the night, as Mike said, thinking about the questions you are investigating. Importantly, you have to engineer your own opportunities, become exposed earlier to the possibilities of research work, and be around smiling people. Thank you very much.

V. CAREERS IN CLINICAL RESEARCH

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Each year, basic scientists make significant discoveries about the mechanisms and processes of disease. These discoveries must be evaluated and used, where appropriate, to develop new methods to diagnose and treat human illness. The observations made in clinical medicine, in turn, need to be fed back to the basic scientists to stimulate and refine further research. Over the last 30 years, while the demand for high-quality, quantitative research evaluating the technological and biological advances in clinical medicine has

Table 15. Myths and Modern Advice

Traditional Advice	Modern Advice
Take the single, well-traveled path to success.	There are many different types of successful research careers and many paths to choose from.
Clinical researchers need to be the expert clinician, and statisticians will run the numbers.	Get formal training in research methods, operations, and quantitative methods.
Working on large, multicenter projects is a bad career move.	Future impact projects will be large, collaborative endeavors, not single-investigator initiatives.
Once you have a successful project, publish as many papers as possible.	Medicine is moving fast, and life is short. One impact paper is worth 100 "variations" on the theme.

increased, the number of qualified, adequately prepared physician-scientists entering careers in clinical investigation has dropped sharply. This is unfortunate in as much as it creates a bottleneck in the process of translating research findings into improvements in public health. Although a career in clinical research has many challenges and involves accepting certain tradeoffs, it offers a unique opportunity to impact the health and well-being of large numbers of individuals.

Clinical research or investigation can be defined as patient-oriented research that involves the whole patient, not just parts of patients or specimens from patients. High-quality clinical investigation uses many different types of tools and is distinguished by a reasonable expectation that one is going to materially improve our understanding of some disease process and its diagnosis, treatment, or prevention. In addition to performing clinical trials, clinical research often employs the methods of outcomes research such as epidemiological studies, cost-effectiveness analyses, and quality-of-life outcomes to reach beyond answering the basic questions of efficacy, effectiveness, and safety in an effort to help further guide clinical decision making at various levels.

We will provide some thoughts about the personal elements necessary for success in a clinical research career, a framework for developing your career, and some consideration of the challenges that a clinical researcher encounters. We also will highlight some of the myths we believe have surfaced around clinical research training and offer our own views of the realities of contemporary career development in clinical research (Table 15).

Personal elements for a successful career. Many of the reasons that people choose medicine as a profession are also inherent in careers in clinical research, and there are general questions that everyone should consider and answer for themselves before embarking on a career. First, is the work going to be worthwhile? Certainly, clinical investigation can offer important, meaningful work that provides the opportunity to make a substantial difference in the lives of patients and in our scientific understanding of an illness. Second, will the compensation be fair? As with any career choice for each individual, the compromises or trade-offs one makes to realize his or her ultimate goals are all part of the compensation formula. Opportunities to work with smart people, flexibility to pursue personal research interests, international travel, or the chance to be on CNN discussing breakthrough research are of significant value to some people. Others prefer more time with family and patients, or pursuing interests outside their primary career. You have to decide what balance meets your goals best. A third question that often arises is will there be appropriate recognition for the work? This, too, is an individual preference, but one that should fit into the context of one's overall goals in life. A principal investigator of a large, multicenter clinical trial of a potential blockbuster drug will necessarily be someone comfortable in the spotlight and who can speak to large public audiences, and this serves as a measure of recognition and accomplishment. Others may desire advancement opportunities at their company or institution where they can broadly influence research emphasis in a particular area. A fourth question is what kind of atmosphere do you desire to work in? Clinical investigation is now rarely an individual endeavor. It is important at the outset to consider what kind of people you envision working with: will you have common motivations, similar goals, and reasonably comparable means of achieving them? For this question, it is also important to give much consideration to what position you want to play on the team. Are you drawn more to generalizations or details? Do you want to lead or follow?

Although there is no single prototype that exemplifies the successful clinical researcher, there are some key personal elements that are generally present. A passion for the work and substantial resilience to failure are core characteristics commonly found in people who are highly successful in their chosen profession, and clinical investigators are no different. However, successful clinical researchers also must be able to formulate good questions. The ability to obtain research funding will largely depend on developing research questions with the potential for substantial impact. Another common characteristic of successful clinical researchers is that they are at least somewhat unreasonable. To make a significant contribution, one often has to be willing to go against the flow, look beyond what is popular or current, and explore what others may consider to be foolish or eccentric ideas. You must also possess the confidence to challenge your own ideas and take a skeptical look at what you have produced. Finally, clinical research is not an endeavor for dilettantes. There is an important body of technical information that one needs to master and a variety of skills that must be developed in order to be a successful, high-quality clinical researcher; these will be discussed in later text.

Developing your clinical research career. Once one has chosen to pursue a career in clinical research, six major steps should be undertaken as part of the preparation process. The first is to define your career specifications.

How much time do you want to spend doing clinical investigation versus practicing or engaging in some other

professional activity? There is a variety of different models at different institutions, and some institutions will not guarantee protected time to do your research.

How do you want to fund your research? If you choose to work in industry or in government, you will have less pressure there. If you choose to work in academic medicine, although you might have more leeway in pursuing your particular research interests, you will have a much harder time getting money to do it. In academic medicine, there are three primary sources of funding: federal grants, industry grants, and foundation grants. Academic institutions rarely have money available to support clinical research. Each funding source comes with its own pros and cons.

What role do you want to take in research? Do you want to be the thought leader, the principal investigator, the person who sits at the head table with people looking to you for the next step in a big clinical trial or project? Do you want to be a clinical site principal investigator, which allows you a seat at the head table, but not necessarily having to lead the way?

What is going to be your research focus? It could be on a disease or condition such as acute coronary syndromes, or it could be on a technology such as echocardiography or interventional cardiology. Do you want to deal primarily with gathering novel patient data or alternatively focus on established datasets?

Lastly, what career path will you choose? Traditionally, the single path to success was to get an early career development award, then an R01, move to lab director, and then on to chief of some department and so on. Today, many paths exist to a successful career in clinical research, even outside academic institutions. Excellent opportunities can be found at federal regulatory agencies such as the Food and Drug Administration, at funding agencies such as the National Institutes of Health or Agency for Health Care Research and Quality (AHRQ), in health care management organizations like Centers for Medicare and Medicaid Services (CMS) or managed care, and in industry.

While it is instructive to outline your career specifications, it also should be with the understanding that it is not to be used as a fixed blueprint of the future. You will likely change course many times throughout your research career, as medicine changes and as you change, and you must possess the flexibility to adapt to the inevitable detours. It is useful, however, to have a guide to look back on after a time and reassess where you are and whether you are still going in the direction you intended.

A second major element in preparing for a career in clinical research is to identify mentoring relationships. You should identify a role model or two who will help guide and advise you on your overall career progression. This person or these people should have a good track record of not only individual research productivity, but also of helping to create successful independent investigators. Your principal mentor also should be senior enough to step aside and let others be the first author on publications. In addition to the principal mentor, it is also necessary to have other people serving in secondary mentoring roles to make sure everything is covered. No one person will be an expert in every skill needed to be successful in clinical research, and you will need to align yourself with people who have essential content or methodological expertise in your field. It is important to recognize this early and form relationships and networks that will help you to grow and that can help guide and support you when you need to cross a bridge.

A third major element is to undertake didactic training in clinical research conduct and methodology. Early training is beneficial, but you may want to consider getting some research exposure first so you get a sense of which electives to pursue. A degree, such as a masters in clinical research or a masters in public health, can be helpful but it should not be considered essential. A fellowship such as the Robert Wood Johnson Clinical Scholars Program also can provide the training, education, and skill development necessary to becoming a successful, high-quality clinical researcher. "Short courses" or conferences alone are not sufficient for development. The core essentials of didactic training to pursue should include biostatistics, principles of clinical research, clinical trial methodology, ethical issues, and research management. Elective elements may include advanced statistical topics, molecular genetics of disease, health services research, or health economics.

Another major element in launching a successful clinical research career is to apprentice on a successful research team. Consider your career specifications and seek out opportunities to work with like-minded people on projects underway. There will be plenty of opportunity to get invaluable hands-on experience if you use your mentoring network and are willing to ask for what you want and then follow through on your commitments. It is no longer considered a bad career move to work on large, multicenter projects as a young investigator. Future impact projects will be large, collaborative endeavors, not single investigator initiatives. In the past, it was believed that the formula to success was to focus on one small area and become the expert in this area. That is no longer the case. There are now opportunities to work in multiple areas and be the bridge between the more narrowly focused experts.

A fifth element in preparing for your clinical research career is to conduct your own research projects. You should focus your efforts on addressing interesting questions that add something new to the literature or knowledge base and are not just replication or "me too" research. The results of your research should have the potential for future clinical impact, although this is often delayed. It is important to have several projects to take ownership of so that you will be writing manuscripts for publication as first author.

Once you have a successful project, you should not feel obliged to publish as many papers as possible on those results (the tonnage approach to clinical research). One impact publication is worth 100 "variations" on a particular theme.

Finally, immerse yourself in the culture of research.

Attend national and international meetings, keep current on the literature in your field, seek new networks and research relationships, and pursue new funding sources and opportunities.

Getting the most out of your clinical research career. If you are already in a training program, you might wonder if you are currently in the right place to continue your career. There are some clues that can help you determine whether or not you are getting the most out of your clinical research training experience. First, is there divisional and departmental support for clinical research training? Without firm institutional commitment and support for the development of high-quality clinical investigators, the push toward performing largely clinical duties may impede your ability to successfully develop your clinical research career. Part of this institutional support should include protected time to learn and perform research. Another indication of whether you are in the right place is if there are appropriate role models and mentors available to you. Are they helping you network, challenging you, advancing your skills, and being generally supportive? Lastly, an institution that has a good record of clinical research trainees going on to have successful clinical research careers is also a good indicator of the quality of its clinical research training program.

What can you do if your institution is not supportive of clinical research training? There is no reason to forego your goal of becoming a clinical investigator if this is the case. One avenue to pursue is to arrange for a two-year clinical research fellowship somewhere else. Contact the National Institutes of Health about clinical research training programs that you can apply for and search the Web for other fellowship opportunities. Consider combining resources. For example, didactic training could be obtained at a public health school or a graduate school. Separate from this, you may become associated with a research group that is willing to take you on as a junior member of the team to work on an interesting problem. Start networking with people who do what you want to do; you can often help create your own opportunities just through being interested and involved. Funding will be the biggest stumbling block. Institutional or individual National Research Service Award (NRSA) training grants may be helpful in providing support for a training fellowship.

Once you have gotten past the preliminary training phase of your career and are ready to look for a faculty position as a clinical researcher, there are several things to take into consideration. A big issue here, as with clinical research training, is to make certain there is divisional and departmental commitment to protected research time. The institution should have enough clinicians to do the clinical work without having to press clinician-researchers into giving up their research time to clinical endeavors. Look for an institution that is willing to support your salary for two or three years while you get your research going and can submit for funding. It is also important to assess whether the institutional leadership (deans and chairs) has a modern understanding of clinical research and supports the multidisciplinary culture necessary for your success.

There are a number of things you can do if you find that you cannot get a job at a clinical research powerhouse. With the ease and accessibility of the Internet, you could consider creating a virtual clinical research enterprise. Ask yourself what strengths you bring to the clinical research table (e.g., patients for randomized clinical trials, technical procedural expertise) and use your network to find a research team looking for your particular ability. You can also network within your own institution to form a mini-team of experts that can partner with outside groups.

Additional challenges to consider. While clinical research is ultimately a highly rewarding enterprise, no review of careers in clinical research would be complete without exploring some of the, perhaps, less desirable aspects of the profession. Perhaps the biggest hurdle in clinical investigation is getting funded for your time and research, and it is a continuous challenge. You will always be working toward getting your next research project funded if you are at an academic institution, which can be a pleasant motivator for successful researchers but often becomes a source of frustration for others. Another problematic issue in clinical investigation is all the paperwork. You hopefully will be successful enough to hire people to help you with that aspect, but you will be ultimately responsible for what gets submitted to your institution and to outside agencies. Much like a tax lawyer, you may have to keep aware of changing government regulations and requirements, and many institutions now require annual certifications for performing clinical research. Finally, you will fail and you have to be okay with that. If you are tempted to use failure as an excuse to retreat to private practice, you may as well go into private practice now.

There are certainly more lucrative pursuits in the medical profession than a career in clinical investigation. There are less frustrating paths to a successful career for a physician. It could take the span of an entire career before one can see the progress that one has contributed to improving medical care. However, if you have the passion and the curiosity for it, and if you want to take part in the evolution of clinical practice, no career is more rewarding than clinical research.

VI. CAREERS IN CLINICAL TRIALS AND EPIDEMIOLOGY: TOOLKIT FOR THE CLINICAL INVESTIGATOR

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There is a basic "toolkit" for those who wish to become a successful clinical investigator. This toolkit includes "fire in the belly," credible clinical skills, certain computer-related skills, and a mentoring environment. You must have each of these four domains because if you miss any of them, it is not

Table 16. Human Research Resources on the Internet

National Institutes of Health Office of Human Subjects Research (OHSR) http://ohsr.od.nih.gov/
United States Department of Health & Human Services Office for Human Research Protections (OHRP) http://www.hhs.gov/ohrp/
U.S. Food and Drug Administration Guidance for Institutional Review Boards and Clinical Investigators 1998 Update http://www.fda.gov/oc/ohrt/irbs/
Bioethics Resources on the Web National Institutes of Health http://www.nih.gov/sigs/bioethics/index.html

going to work out all that well for you. Let us take each of these separately.

First, as part of your own genetic makeup, you have to have fire in the belly. As Eugene Braunwald, MD, FACC, said at an American College of Cardiology meeting in 2003, "Enter a career in clinical research only if you are truly curious and feel the thrill of the chase." In other words, research is not something you do because somebody told you it should be done. You must decide that clinical research moves and inspires you. Also, Dr. Braunwald went on, "Research (that is, answering the question) should be an end in itself, not a means to an end (promotion, recognition)."

Second, you cannot be a good clinical investigator unless you have credible clinical skills. No one will listen to you in terms of the preparation and design of clinical trials if you do not know how to take care of patients and understand clinical problems. This is not difficult because you are all in training situations where you will acquire those clinical skills, but you must maintain these skills if you desire a career in clinical investigation.

Moreover, as Dr. Braunwald points out, you must guard your time available for research jealously. He said, "Clinical excellence is essential for a clinical investigator, but excess clinical duties during your fellowship can prevent you from acquiring the substantial skills required of a clinical investigator." Similarly, if you are constantly in the lab without the protected time to do clinical research, it will detract from your development as a clinical investigator.

The third element in the toolkit of a successful clinical investigator features skills pertaining to computers and the digital world. You must be able to do literature searches, which are getting easier given the advances in computer technology, electronic publishing, and grasp digital library techniques. At the outset, make sure you abide by all human research regulations, which are readily available on the internet (Table 16). There are also minimum requirements relating to biostatistical skills, including concepts of trial design, basic techniques of data analysis, and familiarity with meta-analysis, decision analysis, and cost-effectiveness analysis. However, do not make the mistake of relying on analysis when there are weaknesses in your research design. As biostatistician David DeMets, PhD, said, "No clever analysis can rescue a bad or flawed design." You must have a foundation in biostatistics or you risk making critical errors in the interpretation of data. Finally, once you have finished your research, you must be skilled in writing it up and presenting your observations.

The fourth and final component in the clinical investigator's toolkit is the mentoring environment. None of this will work and flow easily for you unless you live and work in an environment where there is a strong mentoring, nurturing philosophy.

Trial design. If you hope to be a credible clinical investigator or epidemiologic researcher, your basic core curriculum must include concepts of trial design. Most of what we do in clinical trials is to compare treatment groups; often we count the number of patients in treatment group A versus those in treatment group B who experienced an event or who reached a primary end point that allows us to compare the groups. At times our analysis is based on time to events using life-table methods or the Kaplan-Meier methodology.

It takes time to develop a clinical trial; it requires thinking through all the implications of a particular analysis. Those of us involved in the Thrombolysis In Myocardial Infarction (TIMI) study group, for example, have started a major clinical trial that is scheduled to enroll 13,000 patients. This is a trial comparing clopidogrel, the most commonly used thienopyridine following percutaneous coronary intervention, with a novel thienopyridine that may offer advantages over clopidogrel. It took us 1.5 years to design this clinical trial.

When defining a question to study, it should be clinically relevant as well as sensitive to the treatment effect you are investigating. Complete ascertainment of patients who are enrolled in the trial is very important. If you have missing data, you detract from your power to make an observation about any differences that might or might not exist between treatments. If it is a regulatory trial, agencies such as the Food and Drug Administration (FDA) are going to do a worst-case-scenario analysis; if you fail to ascertain all data involving patients, the FDA reviewers will assume the worst case scenario and conclude that all your dead patients were in your investigational arm so that they do not end up approving something unsafe. Also, the information you acquire must be resistant to biased assessment. This is why we often use clinical events committees, for example, who are blinded to treatment assignment to make official determinations about whether events occurred. Then, based upon their assessment, the primary end point is analyzed. Clinical events committees are very important forums, which are pivotal to clinical trials.

Meta-analyses provide the kind of information we use when we are working on guidelines. Understanding how the data have been pooled is very helpful as a clinical investigator. For example, you can conclude that there is a treatment effect, but you never know exactly what the effect is; you are always estimating it, and any estimate of

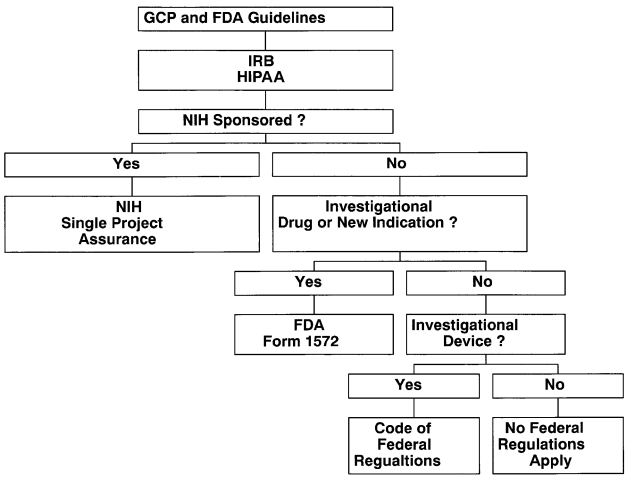

Figure 4. Regulations governing human research. With permission from Circulation 2004;109:2672–9. FDA = Food and Drug Administration; GCP = good clinical practice; HIPAA = Health Insurance Portability and Accountability Act of 1996; IRB = Institutional Review Board; NIH = National Institutes of Health.

treatment effect must recognize that not every patient within a given trial responds the same way, so there is within-trial variability. The Oxford group has popularized this, and it is referred to as the fixed effects model. At the Harvard School of Public Health, it was suggested that not every trial gives you the same information, because there may be subtle differences in patient populations or protocol, leading to between-trial variability, which is the random effects model. If the trials are homogenous, it collapses back down to the fixed effects model.

Required reading. There are three resources that I consider required reading for the clinical investigator. These books explain much of what I have reviewed here. They include the classic Stanton Glantz book, *Primer of Biostatistics* (6), which now includes a CD-ROM that allows you to actually run all those statistical routines I have mentioned here in passing. *Fundamentals of Clinical Trials* is an excellent book by Lawrence Friedman, Curt Furberg, and David DeMets (7) that discusses the fundamentals of clinical trials and power calculations. Diana Petitti's *Meta-Analysis, Decision Analysis, and Cost Effectiveness Analysis* (8) is very readable. Its subtitle is *Methods for Quantitative Synthesis in Medicine*, and it explains the equations of research and how to calculate data using worked examples.

You do not have to worry about buying a complete statistical package to actually perform some of these runs. There are free public access domain websites, for example, http://home.clara.net/sisa/index.htm, where you can do statistical analysis directly on the Internet.

Also, it is important to be aware of the regulations governing human research and particularly the attention paid to patient safety (Fig. 4). You have to know whether or not you are doing research that involves treatments governed by FDA guidelines. The code of regulations and guidance provided by the FDA to investigators and to sponsors of trials can be accessed at http://www.fda.gov/opacom/morechoices/industry/guidedc.htm, and these are also available on public domain access websites as well. I mentioned other internet sites featuring guidelines for doing human research (Table 16). I recommend you review these if you are seriously considering a trial in clinical investigation. There are excellent commentaries and guidance produced by the FDA, the National Institutes of Health (NIH), and others that will help you design a clinical trial that meets regulatory requirements.

Presentation skills are important, of course, and one good book to consider when working on your writing is Ed Huth's *Writing and Publishing in Medicine* (9). He does a terrific job of outlining the structure of a scientific paper. Be aware that all the major cardiology journals now require electronic submissions, and you have to know all the specifics of what the individual journal expects. For example, you cannot just keep writing endlessly; there are word count limits on papers submitted to the journals, as well as limits on the number of figures, tables, and references. You also must declare your relationship with industry or any conflicts of interest. You must be prepared to go through multiple drafts. Personally, I am not really comfortable with a manuscript until I have been through three to five drafts, and Dr. Braunwald has said that 7 to 10 may be necessary because you have to keep writing until you really have it down correctly. Of course, once you have submitted the paper, you have to be able to respond to reviewers, a very important skill.

Besides print skills, you need to consider your oral presentation skills. Before you make your presentation, you must be thoroughly familiar with the topic. Always adhere to rules for slide preparation; for example, limit the number of lines of text on the slide. Make sure you rehearse—with and without slides, with and without a pointer. If you take the time to rehearse and you consider what can go wrong, you probably will not panic if something does indeed go wrong during your presentation. Always start your talk by looking in the center of the back row. By gazing out that way, you engage the whole audience; then you can start visually "walking" around the audience in quadrants, allowing your eyes to move from one quadrant to another.

Career goals. Finally, I want to discuss career goals. I agree with Dr. Braunwald who advises that you choose your laboratory, research group, or mentor carefully. A "big name" is not necessarily a great mentor. There are resources on mentoring in cardiovascular science, including a mentoring handbook available through the American Heart Association (http://www.americanheart.org/presenter.jhtml?identifier=3016094).

Also, according to Dr. Braunwald, accept your first faculty position only if it will allow you to devote at least two-thirds of your professional effort to clinical research; anything less is likely to stunt your growth as a clinical investigator. Furthermore, align your research and clinical activities. For example, cloning of gene-encoding ion channels, research in clinical electrophysiology, and care of

patients with arrhythmias is a good alignment of goals. If you clone genes encoding ion channels and then conduct population research that has nothing to with that, you are not synthesizing your efforts into a meaningful, cohesive direction.

The focus of your investigative efforts should be to devote yourself to the study of a clinical problem or disease and stay with it. Do not become a slave to a single technique, but master whatever techniques are necessary to address the problem. I knew nothing about various biostatistical techniques when I started my career in clinical investigation; I developed them one by one, taking courses, reading books, and working my way through it.

Conclusions. There are important differences in the types of research done in cardiovascular medicine. In basic research, mechanisms are valued the most; in clinical investigation, it is the outcome. For an epidemiologic investigator, prevention from a public health perspective is the most valued part of research. The research strategy for the basic scientist is to control all the variables so that you can actually test the one thing you are interested in and eliminate the number of degrees of freedom. We cannot control all the variables when we are doing clinical investigation, so we randomize one variable and enroll enough patients so that hopefully matching occurs in the groups enrolled in the study. Public health epidemiological investigation matches everything except for one variable to see if that one variable is truly impacting on the health of the particular point of interest. All of this requires very few events if you are a basic scientist; maybe all you need is 20 events, so the sample size is a lot smaller. But for clinical trial research, we may need 5,000 to 20,000 patients to get the necessary power to actually observe whether there is a statistically different significance. From the public health perspective, if you are an investigator you will likely need far more than 20,000 patients; more likely, you will need a study group along the order of magnitude found in the Framingham Heart study to make reliable public health observations.

Please, do not get discouraged if you do not knock the ball out of the park the first time at bat. However, you should question whether clinical research is the best career for you if you have nothing substantive to show two or three years after you have completed your research scholarship training. Remember that even if you do not continue as a clinical investigator, your experience in clinical research will greatly enhance your abilities both as a teacher and a clinician. Even if it does not work out, it will be very valuable time that you have spent.

Question and Answer

Question: I am an interventional fellow at Seton Hall University and a foreign medical graduate. Coming here, I have an ambition to achieve the best I can in this country. I already am an internal medicine doctor, and I am trying to pursue a career in cardiology. I finished my residency and am looking for a fellowship. This has turned out to be very difficult because I am a foreign graduate. I was told by one university that they would not even consider my application. So I looked for ways to advance my career, found a research fellowship, and discovered that I loved it! Now I am a U.S. citizen and am looking for a job. That too has turned out to be difficult. I cannot navigate around to find how I get connected with academia. So I am still looking for my academic career, but it is not as easy as I thought it would be.

Dr. Fuster: If you want to pursue such a career, you really have to focus a lot. In other words, I would not just say, "I need an academic job at an academic institution." If you go there with a specific goal, a specific project, specific focus, you have a much higher chance.

Dr. Antman: I agree. You clearly demonstrated the first part of the toolkit, which is the fire in the belly. Without that, the rest of this conversation would not be taking place. Focus is extraordinarily important. If you go in with a very diffuse concept, it will be highly unlikely that you will have much success getting an academic position. Identifying a niche where you can provide some experience, some expertise, some resources that are missing in a particular academic environment will be much easier. Think about what excited you most in the work you have done up to this point.

Question: Realistically, for those of us who are one or two years out of graduation from our fellowship, it is hard to say we have an area of focus. Also, your focus in research changes by your mentor and by what institution you go to, so there is a fusion we have to go through. But let us say I have a focus. It is still premature, and I take my first job as junior faculty. Then pharmaceuticals knock on my door telling me to enroll patients in all these protocols, saying that could be a way to get into clinical research. Another way to possibly get my turn would be to say I want to analyze the data from different perspectives. So, you have got some competing ways as a junior person trying to find a focus. Where can you go?

Dr. Antman: These are very perceptive points. It is perfectly acceptable to take stock of where you are at a given moment in time and say, "Have I actually got the right focus here, or should I be making a 30-degree change in where I am going to be spending my energies and efforts?" I did that myself; I had spent quite a bit of time involved in clinical trials on antiarrhythmic therapies to suppress recurrences of atrial fibrillation. I became very convinced that I was interested in clinical investigation and clinical trial work, but I evolved more and more toward investigation in acute coronary syndromes. So I redirected my original focus when other opportunities became available, and I realized that this excited me even more.

I do want to caution you about the barrage of pharmaceutical and device manufacturer trials. That is because we live and work in an environment where there is conflict of interest with those sponsors in terms of their product with respect to clinical investigation. If, however, what you are

talking about is getting involved in a clinical investigation that may be industry-sponsored, that is perfectly fine as long as it is through an environment where you have the academic links. I am specifically cautioning against just signing on to be an investigator for a clinical trial that is industry-sponsored for which there is straight reimbursement for recruiting patients, but there really is no return in terms of your career development for that effort.

VII. CAREERS IN OUTCOMES RESEARCH

Harlan M. Krumholz, MD, SM, FACC (Departments of Medicine [Section of Cardiovascular Medicine, and the Robert Wood Johnson Clinical Scholars Program], and Epidemiology and Public Health, Yale University School of Medicine, and the Yale-New Haven Hospital Center for Outcomes Research and Evaluation, New Haven, Connecticut)

Outcomes research is the study of the end results of health care. All studies have outcomes, but what distinguishes this field of research is that it aims to describe and improve the final result of clinical decision-making and health care delivery, with particular emphasis on the patient's perspective. Outcomes research focuses on what is ultimately achieved by our efforts in health care. This applied research seeks to align the needs of patients with the performance of clinicians and the health care system to produce optimal outcomes with the available resources.

Interest in outcomes research is growing, as practitioners and policymakers increasingly appreciate the importance of rigorously examining how health care is delivered in order to achieve the best results. We are in the midst of a rapid expansion in diagnostic and therapeutic options for our patients. At the same time, health care costs continue to rise, placing great stress on those who are paying for care and affecting the national economy. We need research that defines the best patient-centered, clinical strategies and provides insight about how to move established knowledge into routine clinical practice.

Outcomes research is not based on a particular methodology, but rather is defined by the type of questions it addresses. The questions focus on measuring and improving the effectiveness, efficiency, equity, safety, timeliness, and patient-centeredness of health care. As such, the methods are often at the interface of social sciences and medical science, drawing on the methods of clinical epidemiology, biostatistics, health policy, economics, sociology, psychology, business, and anthropology. The perspective spans decision-making at the individual level through policy at the population level. The findings have implications for individual choices about clinical strategies and for broad-ranging health policy. The research has many facets, but is also always oriented toward improving practice and policy.

Outcomes research is the ultimate translational research. Researchers have demonstrated that scientific breakthroughs in the laboratory or even in clinical trials do not necessarily have a favorable impact on population health. The dissemination of the information, the adoption into practice, the effect in real-world populations, the application by real-world clinicians, and the acceptance by typical patients may be variable and lead to results that are different from what was anticipated by the initial reports.

The basic science of outcomes research addresses the need for improved methods of collecting and analyzing data about clinical practice, patient health status, and population health. This basic science also needs to provide new organizational interventions that can promote a more effective and efficient approach to health care delivery. In this context, the advent of electronic health records in particular is an opportunity and challenge as it heralds an era of unprecedented accessibility to detailed information about patients and providers.

The field tends to attract individuals who embrace the challenge of producing knowledge and insights that can be translated into action to benefit patients and populations. The end product is not only a publication, but fundamental improvements in care and health care delivery. Outcomes researchers contribute to the development of decision-making and practice that is firmly embedded in science.

Priority areas. The National Heart, Lung, and Blood Institute Working Group on Outcomes Research in Cardiovascular Disease identified a set of top priority areas for the field (10). This list was not intended to be all-inclusive, but rather to highlight where there is a great need for investment. The top-tier priorities included:

- *Development of surveillance systems for cardiovascular care and outcomes*, referring to the need for continued monitoring of the national patterns of care and outcomes.
- *Promotion of "patient-centered" care*, highlighting the need for studies that would identify the determinants of patient-centered outcomes in people with cardiovascular disease, evaluate interventions designed to enhance health status and quality of life, and incorporate health status into all appropriate clinical trials.
- *Development and translation of "best practices" in clinical practice*, which addresses the need to determine and enhance how well clinical strategies perform in the real world.

The Working Group also identified the following areas that are important to the field: 1) promotion of the use of existing data; 2) facilitation of collaborations with other federal agencies; 3) investment in the basic science of outcomes research, with an emphasis on methodological advances; 4) strengthening of appropriate National Institutes of Health funding agency study sections with individuals who have expertise in outcomes research; and 5) expansion of opportunities to train new outcomes research investigators.

Training. To have the opportunity to make consistent, high-level contributions that can positively influence health

care requires a commitment to gain the necessary skills. There is no single path to attain these skills and true competency will require lifelong dedication to learning, but the effort must be made in a serious and sustained manner. Some people will find the best approach through degree programs while others will find different opportunities. What is important is an eagerness to learn and a willingness to commit the necessary time and energy.

The basic content of training for a career in outcomes research includes: 1) biostatistics; 2) clinical epidemiology and health service research methods; and 3) principles of health policy and management. In addition, knowledge of informatics and economics is becoming increasingly important. Trainees may specialize in specific areas but basic competency in all of the areas is necessary.

Another important skill that does not appear in any formal curriculum is how to ask good questions. Instructors need to foster curiosity in their students and nurture their ability to ask important questions. Students should be encouraged to question conventional wisdom and not readily accept dogmatic statements without understanding the basis for the knowledge. They need to take advantage of their clinical experience in conceptualizing questions that will have meaning for patients.

There is no single best time to start acquiring these skills. For some people the opportunities to commit time to this endeavor occur in medical school, while others will recognize their interest later and pursue it as part of a fellowship or even afterwards. The amount of time that it will take to establish a firm foundation of knowledge in research methods will vary by individual and may be influenced by personal circumstances. What is clear is that the foundation is a critical component to long-term success.

Perhaps the most important component of training is mentoring. Mentors are needed throughout a person's career, but the best training programs will encourage students to develop a network of mentors who can provide guidance about learning strategies, project selection, and career guidance. Programs should encourage the development of local and distant mentors. Having mentors outside the trainee's institution can be very valuable, and certainly no one mentor can accomodate all of one person's needs. The presence of a mentor network allows for broad coverage for the support that is essential to a new investigator.

Careers. Careers in outcomes research range from research to application and service. Within academic institutions, individuals with this expertise can lead efforts to generate knowledge that can evaluate and guide current practice and policy. In addition to research, these individuals often are also involved in local, state, and/or national initiatives to improve health care. The distribution of time may vary, as some individuals may devote relatively more time to service and others more to research. Funding for research is available from many sources, including the National Institutes of Health, the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, the American Heart Association, industry, and various foundations.

This training is also ideal for other venues. People with an interest in service may eventually be strong candidates for leadership positions in academic departments, hospitals, and health care systems. Outcomes researchers also are well positioned to contribute to positions in health policy, including those with local, state, and federal agencies. Industry and consulting agencies have a great need for people who think critically about health care delivery and can interpret and understand the clinical research literature. Foundations and other philanthropic institutions can benefit from people with clinical experience and skills in generating knowledge about practice patterns and population health.

Conclusions. Societal forces are raising the awareness of the importance of elevating clinical practice and health care policy. Outcomes research holds abundant opportunities to evaluate, guide, and improve practice and prepare investigators who are capable of leading positive change. Medicine has remarkable opportunities and challenges in the years ahead. Ultimately its success will be measured in lives that are bettered, an accomplishment that will require a keen focus on improving what we do and ensuring that each patient has access to the very best care. Outcomes research is well positioned to contribute directly to that goal.

VIII. CAREERS IN IMAGING RESEARCH

Robert S. Balaban, PhD (Laboratory of Cardiac Energetics, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland)

Imaging is a remarkably broad field today, ranging from the study of a single molecule, to a cell, to whole tissues—all the way up the scale to the intact human where clinical studies are conducted. In our quest of understanding the interpretation and control of genetic information to generate a given phenotype, imaging provides key information in space and time of many of the key elements of this process. One of the most important advances of the past five years is the ability to extract information at the cellular level within intact tissues or subjects. These advances in molecular imaging are getting very close to melding structural biology, cell biology, and physiology to greatly improve our understanding of basic physiological processes, as well as genetic regulation of these processes.

Developmental biology. If you follow developmental biology, for example, trying to understand how a blood vessel is created or destroyed, you quickly realize that the interactions of cells in space and time are critically important in this and most differentiation processes. So, in order to transfer a stem cell into the heart and get it to replace a damaged region of the heart through regenerative processes requires a better understanding of how these cell-cell interactions occur. Obviously, imaging is going to play a key role in the understanding of this process.

Mapping the human genome has been very important in beginning to understand these developmental processes, but the genome itself isn't the end of the discovery process. This basic network of genetic expression control is what we are going to be working on for the next several decades in biology and medicine. What are the rules guiding development? What controls the distribution of blood cells, or associated nerves?

One great example is a high resolution X-ray computed tomography (CT) scan of the vasculature geometry of genetically identical mice. The question to ask is when do these vasculatures deviate from fixed rules of the genome and are identical to when more "random" distributions of vessels are found obeying more general rules outlined by the genome. In many studies it is becoming clear that only the very initial stages of the vasculature are "hard wired" while the rest relies on more general rules. These general rules could be to obtain a mean oxygen tension in the tissue, or remove a particular metabolite where there are almost an infinite number of solutions to satisfy these rules with how the vessels are placed in the tissue. This leads to what appears to be almost random distribution of vessels since we do not yet understand the general rules applied. Imaging will help us learn what those rules might be and tells us where the more specific genome pattern rules are replaced by more general rules where physiology, environment, and timing start playing a more important role in the process. This type of study, deciding when the genome's influence ends and when the general rules apply and become dominant, is one of the areas where the role of imaging is going to be very prominent.

Imaging is also one of the major readouts in any genomic screen (11). One program is conducting a genomic screen of the mouse, looking for early embryological deficits in structure and function of the heart using a mutagenesis approach. These studies have discovered genetic models for most of the early cardiovascular and in utero diseases in man, and now we're starting to map out which genes may be responsible for those particular events (12).

Stem cells are a hot topic today, and imaging will play a key role in understanding how to place stem cells in the myocardium using an interventional approach. We are using magnetic resonance imaging (MRI) to guide the injection of stem cells into the region of interest within the myocardium (13). Later on we will be able to see labeled stem cells and follow them for weeks to understand how they are differentiating and see that they eventually do contribute to the contractile process. Imaging will play a key role in tracking these cells, monitoring differentiation, and helping us understand what is going on in the myocardium as we try to control cellular differentiation.

Image-guided therapy. We are moving beyond using imaging to deliver therapy. Interventionalists have been using X-ray–based imaging methods to guide the therapy for many years. However, this approach has been generally limited to a view of the vascular space due to the dependence on contrast agents. Thus, the types of procedures that can be attempted are limited by what you can see and potentially even the radiation dose required. With modern imaging tools like real-time MRI to guide procedures, we can now not only get a better view of the tissues that are being worked on but also get immediate feedback on the function and viability of the tissue under repair without any radiation dose. This type of dynamic soft tissue imaging, together with appropriately modified robotics, will allow us to tackle problems we never thought we could in the past.

Imaging: what is the right modality and right spatial scale? A clinical or basic science investigation requires a sound and important biological question to be addressed. To answer this question you must choose the modality that can, or that you foresee will, provide you the appropriate information in the right spatial scale to resolve the key issues. The most successful long-term research programs are driven by the biological or clinical question, not a particular technology or imaging modality. This permits one to adapt or adopt technology as you move forward on your problem rather than search for applications to point a given technology at.

One example of the importance of scale and technology is the study of regional blood flow in the heart. The MRI techniques are now permitting physicians to see small subendocardial perfusion defects in the heart and the question arising is: "how small of a perfusion defect is significant?" Our previous experience in determining the normal distribution of flow in the heart was obtained by chopping it up into little blocks and counting the density of microspheres we had previously injected into the vasculature. These data suggested a wide variation in blood flow of almost two- and sometimes three-fold under a variety of conditions suggesting that flow heterogeneity was normal and not indicative of any vascular pathology. However, we and others noticed early on with high-resolution MR perfusion images that have much higher spatial resolution than the tissue-blocking approach that we observed very little flow heterogeneity in control patients and animal models. This observation was followed by a systematic imaging study of microsphere distribution within the heart at several different spatial scales that revealed the microspheres were not very reliable beyond a cm^3 or so of heart tissue (14).

Another very important development has been the use of multi-photon excitation schemes to observe subcellular events in vivo (15,16). This form of microscopy allows us to go deep into tissues while maintaining the resolution we need to examine a single cell with a microscope; this gives us a 1- to 2-μm spatial resolution deep ($>$300 μm) in the intact animal. Functional imaging with subcellular resolution using this type of approach is going to become an incredible basic science tool. If you have to get down to the cellular origins of a physiological event, this technology is going to play a major role. For example, the myosin head group angle, sarcomere length, and overall fiber orientation

of muscle cells in vivo can be determined using this approach. In vascular biology, endothelial cells can be observed in vivo along with physiological information including their intracellular Ca^{2+} levels, membrane potential, receptor-binding or protein expression, and a great deal more. This can be directly coupled to measures of the diameter and flow within the vessel containing the endothelial cell attempting to evaluate the functional importance of intracellular events on a given vascular process in vivo. This remarkable imaging approach truly brings cell biology, molecular biology, and physiology together, making it a huge area of research for the next several decades as we start putting the cells and tissues back together into functional and clinically relevant structures.

IX. CAREERS IN ELECTROPHYSIOLOGY RESEARCH

Eric N. Prystowsky, MD, FACC (Clinical Electrophysiology Lab, The Care Group, LLC, Indianapolis, Indiana)

In electrophysiology, there are three broad areas to consider in terms of choosing a research career: clinical electrophysiology, clinical trials, and basic research. Whatever area you select, there are general principles for a successful research career. First, select an area that excites you and is consistent with your skills. Do not select an area of research because your mentor likes it or because someone tells you it is what you should do. The fact is that if you do not like an area of research, you will eventually get bored, lose productivity, stop writing papers, and go into something else. Likewise, if you are not good at what you do, even if you like it, you are going to get very frustrated and quit.

Initially, it is important to stay focused. If you publish five or six papers in an area, people get to know you and accept you as an expert in a specific area. Once you have that kind of reputation, then you can branch out into other areas. However, I disagree with the concept that you should do research in six different areas. Pick something you are good at, something you like, stay focused, and write your papers.

It also is important to ask relevant questions about relevant problems that can be answered in your lifetime. People who say, "I am going to change the world," are very frustrated because the odds are that they are not going to change the world. Focus yourself on what is useful, important, and doable; then you will not get frustrated.

If you want to be a researcher in private practice, you need a skills set. I did not just start in private practice doing research; I had a very detailed nine-year university career before I ever transitioned into practice. If you are really serious about research and it is something that is important to you, you clearly have to start in an academic environment.

You must set your research priorities. If you want a 50-50 split between research and clinical practice, that is a good model. It is also a very popular model. Although universities run the clinical trials, the greatest number of patients is usually enrolled from private practices. Typically, private practices have a huge volume of patients and at least one person who enjoys doing research, going to medical meetings, and developing a reputation as a successful private practice researcher.

Finally, if you do not want to split your time evenly between research and clinical practice, it is perfectly acceptable to set research as a minor priority. With whatever level of research you choose as your priority, remember the skill sets you need. In my opinion these are in descending order of importance. As clinical researcher, you will need to learn manuscript development, abstract development, lecture skills, and grant writing. As a basic researcher, you will need skills in grant writing, manuscript writing, abstract development, and lecture skills. Lecture skills are important because commonly an investigator who has written a couple of influential papers gets invited to your institution, and only then do you realize he or she cannot put six sentences together. As a clinical researcher, your job is to go out and let people know what you are doing.

Why did I put grant writing so low on the list of clinical research skills? Considering the current climate, grant writing for clinical researchers is not high on the skills set list because it is unlikely you are going to have a lot of success obtaining grants. From talking to my colleagues, it is the opposite situation in basic research. Grant writing is probably at the top of the needed skills set for a basic researcher. Indeed, if you cannot get grants, you are probably not going to do basic research. In addition, manuscript writing and lecture skills are important for basic researchers.

Careers in electrophysiology research. If you are looking to participate in clinical electrophysiology research, there are many areas you might want to consider and many questions you should ask.

CATHETER ABLATION. In January 2004 I became the editor-in-chief of the *Journal of Cardiovascular Electrophysiology*. We ask all of our reviewers to consider three questions. The key question is not "Is it true?" but rather, "Does it matter?" It is particularly important to consider "who cares" when considering catheter ablation research. We do not have a good handle on just where ablation fits into a number of medical conditions; thus everyone is going to be interested in research. However, the project has to be in an area where we are going to care about and value the research.

What are the hot topics in ablation research? There is the need to integrate new energy sources and three-dimensional mapping systems into clinical practice. We need more data on computed tomography and how it relates to electrical mapping. Finally, another area in need of further research is new catheter delivery systems.

RISK STRATIFICATION FOR SUDDEN DEATH. This is an area in clinical electrophysiology research that needs more attention. Which test offers high predictability? Most noninvasive tests we have suggest who *does not* need a defibrillator.

The question is who *does* need a defibrillator? The problem is all the false positives that current tests are prone to. This is a major problem, and there needs to be research that will help us hone in on the patients who are most likely to benefit from an implantable defibrillator.

Another important research question is which patients with genetic syndromes require treatment? Which patients with long-QT syndrome, Brugada syndrome, or hypertrophic cardiomyopathy need to be treated? The list of genetic syndromes is long, and the question of which patients require treatment is a hot area of research.

AUTONOMIC NERVOUS SYSTEM. Although there is significant autonomic input to arrhythmias, this is an area that is been sorely neglected by most electrophysiologists.

One of the biggest problems in cardiac electrophysiology relates questions of why certain problems occur. For example:

1) What causes inappropriate sinus tachycardia? It is a fairly common but vexing problem. Patients cannot stand it. It occurs in young people. It remains a terribly frustrating problem because nobody has a good handle on it.
2) Why are there diurnal variations in the onset of arrhythmias?
3) Why does someone have atrial fibrillation one day but none for the rest of the year when the patient has the same substrate and same potential triggers every day?
4) Why is it that someone born with long-QT syndrome and a potassium channel ionic defect lives a completely normal life for 18.5 years and then suddenly goes into cardiac arrest? What happened that day? Why did it occur?
5) Why do people develop neurally-mediated syncope, and how do we treat it?

Some of the questions are very simple, but the answers have evaded us. Unless you are an electrophysiologist, you may not even know this, but patients often tell us that bending over initiates an arrhythmia. Interestingly, in my experience, this occurs mostly in atrioventricular (AV) node re-entrant tachycardia or AV re-entry associated with Wolff-Parkinson-White syndrome. What is it about those arrhythmias that make people susceptible when all they do is bend over? We have no idea, although there are probably clues here that would help us understand why arrhythmias occur. The problem is that nobody has tried to investigate these topics.

IMPLANTABLE DEVICES. Everybody is excited about cardiac resynchronization therapy (CRT) for heart failure. However, there are a number of important questions to be answered regarding the utility of CRT.

1) Which patients derive the most benefit from CRT devices?
2) How do you optimally pace these patients?
3) What is the optimal pacing site or sites with CRT?
4) What is the optimal pacing mode with CRT?

If you like device research, I would focus on CRT because we are just starting to explore this area and because it is going to consume investigators for several years.

ATRIAL FIBRILLATION. There is an endless list of questions in the area of atrial fibrillation (AF).

1) Why does AF occur?
2) What is the link between increased vagal tone and AF onset?
3) Which patients with heart disease are suitable for catheter ablation?
4) What is the optimal catheter ablation method to cure AF?
5) Which patients do better with rhythm control?

There are countless questions that need to be answered with AF, and I suggest you go after them.

VENTRICULAR TACHYCARDIA. Ventricular tachycardia (VT) is not quite as popular a research topic today because VT is easily treatable. You put a defibrillator in and that solves much of that problem, but there are many questions regarding VT that are still unanswered and are means for plenty of research opportunities.

1) What is the mechanism of VT in structurally normal hearts?
2) What is the triggering mechanism for VT in stable ischemic scars?
3) What is the triggering mechanism for sustained VT in ischemic cardiomyopathy?
4) What is the best method to cure unstable VT using catheter ablation?

There is a lot of interest in using catheter ablation to treat the particular VT-causing substrate. This topic is just starting to be investigated and could be a really burgeoning area for research.

Getting research experience. If you are in clinical practice, you can get involved in research through nonindustry-sponsored multicenter randomized trials. Even if you do not have a lot of research experience, you can become involved with clinical trials because many studies need to enroll a large number of patients. In addition to enrolling patients for a specific trial, you can become involved in writing the paper from the study.

Industry-sponsored clinical trials are other opportunities to gain research experience. Often the questions generated for these trials are usually straightforward and focused.

Industry-sponsored clinical trials can be enjoyable. You are offering your patients new therapies in which you are among the first to discover new information and potential benefits from the studied therapy. Additionally, industry-sponsored trials provide an opportunity to network with experts in your particular field of interest.

The field of molecular biology is where the most innovative and impactful research is being performed today and will be for the foreseeable future. It is critically important to gain a better understanding of how certain arrhythmias start.

Because I am not a basic researcher, I would not be the

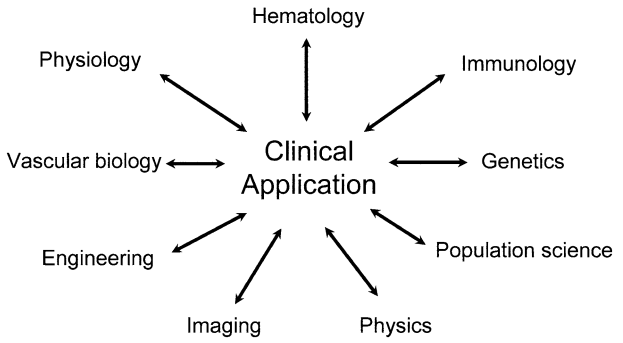

Figure 5. Overlapping disciplines. Translational invasive research involves not just cardiology but also overlapping disciplines and cross-talk between disciplines that may impact clinical applications.

person to give you advice on what areas of basic research you should be considering. However, if you want to do basic research, the best advice I can give you is to find a mentor you trust who does basic research in the area you want to become involved in. Sit down with your mentor and ask for advice regarding which areas of research have the greatest merit for future research.

Never allow your own lack of understanding regarding a specific technique to hurt your research. Instead, bring in an expert who could help you find the missing pieces to the puzzle. Do not think you have to do it all by yourself. Collaboration is often key to answering the most important questions.

X. CAREERS IN TRANSLATIONAL INVASIVE RESEARCH: CONFUCIUS, FRACTALS, AND RELATIVITY

James J. Ferguson, MD, FACC (St. Luke's Episcopal Hospital, Texas Heart Institute, Baylor College of Medicine, and the University of Texas Health Science Center at Houston, Houston, Texas)

"The essence of knowledge is: having it—to apply it; not having it —to confess your ignorance."

Confucius

"The hardest thing of all is to find a black cat in a dark room, especially if there's no cat."

Confucius

What is translational invasive research? The traditional response has been that "translational research" involves taking new understanding from the basic science laboratory and bringing it forward into the world of clinical practice, the proverbial "bench-to-bedside" process. In reality, translational research can involve taking problems that arise at the bedside, bringing them to the bench to tease out some new mechanistic understanding, and then coming back to the bedside to apply this knowledge to the original clinical problem.

The logical inference is that to perform meaningful translational research, you have to truly understand the potential clinical utility of your subject matter. That means an intimate acquaintance with real-world clinical care. This is not bench research for bench research sake—this is bench research that has tangible ties to the bedside. True translational research requires the application of some aspect of bench research, some new mechanistic understanding, for example, that can be applied clinically. While you may not have to be the world's foremost bench researcher, you do have to understand the underlying physiology and how it may relate to and overlap with underlying clinical applications.

Areas of overlap. There are many scientific areas that may have specific invasive applications (Fig. 5). Translational invasive research involves reaching out and overlapping with a variety of disciplines.

This requires forging new conceptual linkages that parallel the complexities of the overlapping biological processes and pathways. My own career is a case in point. I did not start out my academic career in the field of coagulation; I started out researching complex hemodynamics. However, after coming to the Texas Heart Institute and seeing the application and relevance of coagulation to interventional cardiology, I asked some very simple questions relating to the coagulation status of patients coming in for coronary intervention. Simple, mundane questions like, "How should we be utilizing a bedside marker like the activated clotting time to guide coronary intervention?" From this simple application of a bedside coagulation monitoring device, whole new areas of application and understanding began to open up, and the world of coagulation became linked to the world of platelets and inflammation, endothelial function and homeostasis, and lipids and atherosclerosis (Fig. 6).

It is like a vast intellectual fractal network: the closer you look, the more detail (and interactions) you begin to see. And as we consider something as seemingly mundane as antithrombotic therapy, we discover that it has the potential to interact with numerous biologic processes, and vice versa. Something simple—coagulation in the cath lab—now pro-

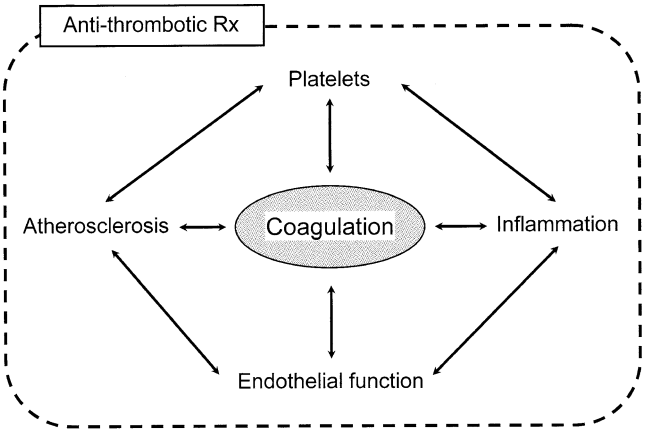

Figure 6. Translational invasive research relies on overlapping disciplines and the forging of new linkages. In this case, various influences affect and are affected by coagulation; therapies that affect one of these factors (such as antithrombotic therapy) may have consequences that extend beyond their primary actions.

Table 17. Do's and Don'ts for Clinical Investigators

Do	Don't
Keep reading; keep learning	Assume anything
Teach—expand your horizons	Lose credibility
Find a mentor	Be afraid to be wrong
Work collaboratively	Get lost in the politics
Write down new ideas	Get lost in the cath lab
Get good clinical training	Get too narrowly focused
Follow through	Just depend on the NIH

vides us an entry into the whole complex world of vascular biology.

A recent series of articles in *Circulation* (17,18) summarize the complexities of coagulation, inflammation, endothelial function, atherosclerosis, and vascular biology. This is exactly the kind of overlapping fractal complexity investigators have to have their intellectual arms around as they enter into translational invasive research. No, it does not have to be *just* inflammation or lipids or platelets or coagulation. Rather, it helps to begin to have a grasp of how they all fit together, recognizing that while there may be no absolute unifying theories, there are a number of intriguing alternative hypotheses.

The world of peripheral interventions continues to grow. The atherosclerotic solar system does not just revolve around the coronary circulation, there is the entire vascular tree, not just on the arterial side, but the venous side as well, an area long neglected by vascular biologists. Some very exciting work is being done with bone marrow stem cells and autologous stem cell injections, both for acute myocardial infarction and for heart failure. Valve repair and even valve replacement are being undertaken percutaneously. A variety of novel therapies to reduce the injury associated with myocardial infarction are now in clinical application. And while cooling and distal protection did not work all that well, this work has provided very exciting new insights into the biology of the vessel wall that will set the stage for a number of potentially fruitful future studies. New diagnostic technologies are emerging, expanding on intravascular ultrasound (IVUS) and optical coherence tomography, including new image processing algorithms, "virtual histology" IVUS techniques. And last but not least, exciting new interventional applications such as left atrial appendage closure devices are finding wider acceptance. Each one of these "hot" topics involves some sort of invasive translational research, taking new advances into the catheterization laboratory.

Next year, the list will no doubt change. When considering an academic career in translational invasive research, maybe today's "hot" areas do not really matter all that much, because the field is moving forward so rapidly. But I would submit that you still have to look at the here-and-now to figure out where the there-and-tomorrow is going to be.

Advances will be made, and these advances will lead to additional questions, particularly through translational research, which is not just providing the answer to a question, but rather it is the process of answering the question that raises more questions which, in turn, raise still more questions. The clinician-scientist is integral to this process because we must take bits of information and integrate them together, to hang them on an underlying conceptual physiologic framework. It is not just collecting the facts—it is translational research that is putting them together.

Do's and don'ts. There are practical "do's" and "don'ts" for the budding investigator (Table 17). These recommendations consider what we should be doing or *not* doing if we are going to be successful. From my own about-as-far-from-omniscient-as-you-can-get perspective, the things young investigators should be doing would be as follows: first, keep reading, keep learning. If you stagnate, if you ossify intellectually, you will be a dinosaur in about two years. Take the time to teach, and not just always the same old things. Extend yourself; learn and teach about new physiologic pathways and mechanisms. You will never learn anything quite as well as when you have to stand up and lecture about it.

Find a mentor and work collaboratively. Productive research depends on teamwork. Write down new ideas—one thing that I have done over the years is to keep a folder of ideas that pop up from time to time (some good, some bad, but all new), and then review them from time to time to see if they are any better or worse or any more or less relevant. As I mentioned before, if you want to do meaningful translational research that carries to the bedside, you have to have a solid foundation of clinical training, so get the good clinical skills you need. Finally, to be successful, follow through; carry your projects (and papers and grants) all the way through to completion.

Now, the don'ts: what should you *not* be doing? First, do not assume anything—things are not true just because everybody says they are true. Do not lose your credibility—it is probably the single most important academic asset you have. Do not say things because people expect you to say them—say things because you believe them. Your audience can tell the difference. Do not be afraid to be wrong. I have

Table 18. Key Skills for Clinical Investigators

- Interventional skills (±)
- Clinical skills
- Academic skills
  - Reading (cross-discipline literature)
  - Riting (manuscripts, grants, presentations)
  - Rithmetic (statistics, trial design)
- Intellectual skills
  - Curiosity
  - Synthesis
  - Discipline
  - Integration
- Interpersonal skills
  - Collaboration/individuality
  - Leadership
  - Patience
  - Sensitivity
  - Integrity

been wrong many more times than I have been right, and I always learn more from being wrong and recognizing it than from being right. It is good to remember that while Babe Ruth once held baseball's home run record, he also holds the major league record for strikeouts.

Do not get lost in the politics of your day-to-day work. Also, do not get lost in the cath lab just doing lots of procedures, while that may be rewarding and fun, translational research looks beyond what you are doing at the moment to think more broadly about what you are doing. From a translational standpoint, there is a risk in getting too narrowly focused because one also may have to reach out to other scientific perspectives as well. Paradigms change and pathways expand, converge, and diverge—you need to be more than a "one-trick pony." And, ultimately, do not just depend on the National Institutes of Health or the American Heart Association or the American College of Cardiology for funding; there are other funding opportunities, including industry, that need to be considered.

Marketable skills. What about the skills that you need as a clinical researcher? Obviously, for invasive translational research, great interventional skills are a plus, but they are not a sine qua non. You do not have to be a superb interventionalist, but you do have to have clinical skills and a solid clinical perspective (Table 18).

Required academic skills include the three R's of academics. However, in our case reading, 'riting, and 'rithmetic become the reading of cross-discipline literature; the writing of manuscripts, grants, and presentations; plus the arithmetic of statistics and clinical trial design. Other skills required in this field are a number of intellectual skills: curiosity, synthesis, discipline, and integration. Importantly, do not forget the oft-neglected interpersonal skills, including your ability to collaborate, your work ethic, your leadership skills, your ability to teach and be a mentor yourself, and, most importantly, your integrity.

Conclusions. As we look at the evolution of interventional therapy—from the old days of balloon angioplasty, to directional atherectomy, to lasers, to rotational atherectomy, to stents, to distal protection, to drug-eluting stents—we begin to appreciate the bigger-picture perspective. With time, our adjunctive therapies have come to include glycoprotein IIb/IIIa antagonists, the thienopyridines, low-molecular-weight heparins, and direct thrombin inhibitors. As we look at our ever-evolving "standard" of care, we have come to recognize that there is always room for improvement; we do not have all the answers, and there is always more to learn.

As clinician investigators we hopefully will continue to ask those questions. From a scientific perspective, we only see half of the picture; the other half of the picture is the clinical application. The essence of translational research is to put the two of them together to form a whole, and to appreciate that even the whole picture is not the final word, but is really just a complex fractal array that can be put together—and taken apart—in a number of different ways.

XI. PANEL DISCUSSION: MOVING BEYOND THE CLINICAL EXPERIENCE—SPECIALIZED RESEARCH OPPORTUNITIES: PART 1

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C. Willaim Balke, MD (Division of Cardiology, University of Maryland School of Medicine, Balitimore, Maryland)
Robert O. Bonow, MD, FACC (Northwestern University Feinberg School of Medicine, Division of Cardiology, Northwestern Memorial Hospital, Chicago, Illinois)
James J. Ferguson, MD, FACC (St. Luke's Episcopal Hospital, Texas Heart Institute, Baylor College of Medicine, and the University of Texas Health Science Center at Houston, Houston, Texas)
Valentin Fuster, MD, PHD, FACC (Zena and Michael A Wiener Cardiovascular Institute and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center, New York, New York)
Eric N. Prystowsky, MD, FACC (Clinical Electrophysiology Lab, The Care Group, LLC, Indianapolis, Indiana)

Dr. Bonow: Bill, what is your take on whether we should be recommending that fellows participate in multicenter clinical trials for their research experience?

Dr. Balke: That question comes up every year, and there is no absolute right or wrong answer. The positives for working on a clinical trial while a fellow relate to the exposure and experience of getting involved in the wave of the future—and that is team research. The disadvantages mostly relate to the fact that you are not going to get identified with the project to the same extent if it was your own single-center study at your own institution. The short answer is: the most important thing is to learn research skills. If you have the opportunity to get involved in a really interesting multicenter trial, where you are going to be contributing at an intellectual and substantive level, then that is reasonable.

Dr. Bonow: Terry, do you want to add to that?

Dr. Ferguson: You should look at doing research as the opportunity to acquire a skill set. Of course, you do not necessarily need a skill set of taking histories, doing physicals, and filling out case report forms. But you do need an intellectual skill set and an opportunity to pose questions, formulate hypotheses, write abstracts, prepare manuscripts, and present findings. So, I view it as an opportunity to get your feet wet. We all know that there is no shortage of institutions out there that use fellows as a cheap source of labor to generate case report forms. That is not a particularly rewarding activity; however, if there is a legitimate chance to

participate in clinical trials and do more of this intellectual work, then participating in a multicenter clinical trial provides real opportunities. It also gives you a chance to begin to network with the players, to "sit at the table" and begin to get involved with this process of making yourself known and developing your skill set.

Dr. Bonow: Your take-home message seems to be to explore ahead-of-time exactly what your role is going to be and be sure that you are going to be gaining from the experience either a skill set or a networking opportunity or both, not just the opportunity to do grunt work. Eric, did you want to add to that?

Dr. Prystowsky: I take a slightly contrary view. If you want to be a clinical trialist: fine . . . but not if you are trying to develop a research career. As I said in my talk, you are far better-off finding something you like to do, defining the area, and doing projects; otherwise, you will not get known. On the other hand, investigators have come out of Duke that you all know because they did research in an area. If you are not sure what you want to do, and there is a way to get your feet wet working on a multicenter trial, fine. But, if you more-or-less know your field and it is not clinical trials, my advice would be stick to your field and do not get roped into that. You are not going to be a player in those trials, quite honestly, unless you grow up in the field.

Question: Do you think there is enough advocacy within the cardiology community for international medical graduates (IMGs) who are here on visas and who all have to leave the U.S.?

Dr. Al-Sheikh: No, I do not think there is enough advocacy. We have to realize the importance of IMGs, who receive their medical degrees outside the U.S. or Canada and come to North America for advanced training. We need to do more. The primary obstacle—and I think you all agree with me—is the immigration law. We need the IMGs. In a New York survey, if you look at the percentage of IMGs who want to go back to their country of origin, they found nobody wanted to go back.

Unfortunately, since September 11, 2001, IMGs hoping to continue their careers in the U.S. have faced more restrictive immigration policies. The law makes it difficult for them to come here and stay permanently, because it wants them to go back to their countries of origin, but we need them. If we believe there is a real shortage in the workforce in cardiology, wait and see: it is going to get worse. And if we do not solve this problem—IMGs comprise 30% to 40% of all cardiology trainees (19)—it is going to be a major problem in the future.

Dr. Bonow: I would emphasize that you should get involved with the American College of Cardiology, because that is where the whole workforce issue is front and center. It is addressed in the new Bethesda Conference report on cardiology's workforce crisis (http://www.acc.org/clinical/bethesda/beth35/index.pdf).

Question: I have a couple questions for Dr. Balke about the K08 award. You noted that the award rate level is somewhat different per the National Institutes of Health (NIH) institute that is granting the K08 award. Sometimes grant applications can apply to various institutes. Does the applicant decide which study group is going to review the application, or is that determined at NIH? And secondly, if you are a faculty member who is getting salary support as part of your clinical activity and you receive a K08 award, what influence do you have on how the money is spent? Do you have to take any of that as salary, or can it all be used for equipment or salary support for a laboratory technician?

Table 19. NHLBI: Divisions of Intramural Research

Laboratory research program
Biochemistry and Biophysics Center
Laboratory of Biochemistry (LB)
Laboratory of Biophysical Chemistry (LBC)
Laboratory of Cell Signaling (LCS)
Cell Biology and Physiology Center
Laboratory of Cardiac Energetics (LCE)
Laboratory of Cell Biology (LCB)
Laboratory of Kidney and Electrolyte Metabolism (LKEM)
Laboratory of Molecular Cardiology (LMC)
Genetics and Development Center
Laboratory of Biochemical Genetics (LBG)
Laboratory of Developmental Biology (LDB)
Immunology Center
Laboratory of Molecular Immunology (LMI)
Clinical research program
Branches
Cardiovascular Branch (CVB)
Cardiothoracic Surgery Branch (CSB)
Hematology Branch (HB)
Laboratory of Animal Medicine and Surgery (LAMS)
Molecular Disease Branch (MDB)
Pulmonary-Critical Care Medicine Branch (PCCMB)

Dr. Balke: The K08 is institute-specific, and that affects the acceptance rates as well as the actual awards. Some institutes award more project support than others. You can send in a cover letter with your application and it can be routed to a specific institute or a combination of institutes. It is easy to see how some cardiology research, both clinical and basic, could cover the National Heart, Lung, and Blood Institute (NHLBI) and the Institute of Aging, so you can specify both.

If you know enough about the study sections, you can request your application go to a study section. In general, most of the institutes have their own K08 study sections, so you cannot subdivide it more than that.

To answer your second question: the K08 and the K23 are salary-support awards. You need to have a minimum of 75% protected time for the research effort, and your salary will be 75% of what your institutional salary is, up to the institute-specific limit. In the NHLBI right now, that is about 75K. You cannot redirect that money into something else; however, your home institution can augment that. So, for clinical activity, you can get money for that work.

Dr. Bonow: I would like to ask Bob Balaban a question. Betsy Nabel was here, and I think she encouraged many people to wonder about intramural opportunities. I ex-

plained how intramural experience at NHLBI was very beneficial to my career. What are the opportunities for people now who are already in a cardiology training program to do something intramurally with NHLBI for a year or more and then go back out into the university experience?

Dr. Balaban: There are training programs in the basic and clinical cardiovascular research as well as special programs in imaging sciences, genomics, and bioinformatics at the NIH intramural laboratories in Bethesda, Maryland. If you come to an NHLBI intramural training program you will be getting an experience from all of the institutes at the NIH, not just the NHLBI. This change in the intramural program has occurred over the last few years as it has become evident that multidisciplinary experiences are required to prepare fellows for the next wave of clinical research areas.

The training programs are an intensive hands-on research experience, perhaps without the same degree of clinical responsibilities as one would have in most other research programs. We have made adaptations to our training program to increase the clinical exposure beyond the rarefied environment in the NIH Clinical Center by opening both an imaging and surgery research program in a community hospital. This permits the clinical fellows to keep touch with the basic practice of clinical medicine as well as guide some of our research projects to very practical issues in a community hospital and not only to what a major teaching hospital experiences.

At the NHLBI Web site (http://www.nhlbi.nih.gov/index.htm), the laboratories and branches of the NHLBI are listed (Table 19). I would encourage you not just to think about the NHLBI, but look at the NIH intramural program as a whole to look for research programs that might be of particular interest to you on the NIH Web page (http://www.nih.gov).

Question: I would like your advice on how to contribute to meaningful research over a career in interventional cardiology? What might be reasonable expectations and objectives to set? Then I would like to direct this question specifically to Drs. Bonow and Fuster: what qualities define a true leader?

Dr. Ferguson: From the standpoint of research in interventional cardiology, you can certainly do more than just perform a whole bunch of procedures. You should look at doing whatever you can to advance the field in some way, shape, or form. But the key is being able to distance yourself from the nuts and bolts of sitting around doing procedure after procedure.

You have to acquire some intellectual skills to be able to look at what you do. In getting back to some of the questions raised earlier about why you do what you do and "Are there ways to think outside the box and do things better?" the interventional laboratory provides you with an opportunity to do a lot of things that we could not do before.

As technology advances, imaging modalities are now coming back into the interventional laboratories. Realistically, you are only limited in interventional research aspects by your own imagination and how you want to do it.

Dr. Bonow: You have to be in a good teamwork environment. It is your responsibility to explore that: for example, "How good are the stem cell people? How good are the thrombosis people?"

Dr. Ferguson: The number of procedures does not matter as much as the scope of the work that is going on and the creativity of the individuals doing the work as well as how aggressively they are pushing the envelope. In terms of your professional development, a lot of that comes back to the issue of mentoring. Look at the people who are there; look at the people you are going to be working with. Are these people who basically come into the laboratory from seven in the morning until eight at night just banging out procedures? Or, are they thinking about and exploring things, using new techniques, and advancing the field? Are they playing with the new toys or collaborating with other colleagues to advance the field? The best advice I can give you as you look ahead and plan your career is look for quality institutions and quality mentors.

Dr. Bonow: As to your second question: how does one pursue a career that will eventually place you in a leadership role? We have all kinds of leaders here today. I doubt if any of us actually started out assuming that we were going to have these roles. We all got into medicine for the same reasons you did. We wanted to take care of patients, but along the way we developed interpersonal relationships needed to become leaders. A lot of this is how you work with teams, how you build teams, how you get self-respect, and how you develop the self-motivation to try to do more.

You must earn the respect of other people. Use your instincts. One of your key objectives, as we have mentioned before, is networking. Networking is absolutely critical, and the mentors you develop now could be the mentors who help you move to the next level of your career and write those letters for you. All of us can probably identify four or five people who helped get us to the next step each step of the way in our own careers. Therefore, getting involved early in the ACC and AHA programs for young doctors allows you to start doing that and begin taking the steps upward. Valentin?

Dr. Fuster: There really is no such career path to becoming a leader. And if this is what you want to be from the beginning, I would persuade you to change gears, because it is not going to work. Ambition for ambition's sake does not work. You should strive to do the work and enjoy whatever research career you want to undertake.

If your question was more general, I would say there are four characteristics to being a leader. The first quality of a leader, to me, is to learn how to listen to and observe people. Once you have that captured, the next step is not to be afraid to make changes, because if you are frightened, you will never be a leader. You have to make changes if you want to accomplish something. The third thing is you have to be knowledgeable. Today, you cannot be a leader if you really

do not understand the nuts and bolts of what you lead. And the fourth is to have ethical standards, which are becoming more and more critical. The role models I always had were people who, to me, had the character and the characteristics of ethics, which was critical to me.

XII. CAREERS IN BASIC CARDIOVASCULAR RESEARCH

Bradford C. Berk, MD, PhD, FACC (Center for Cardiovascular Research, University of Rochester Medical Center, Rochester, New York)

A career in basic science research is like getting a birthday present every day: there is always something new to learn as I wander through my lab and people show me their new data. They are showing me something that didn't exist before, and for me, that joy of discovery keeps me excited and coming back into the laboratory every day. It is challenging and unique; there are fewer than 500 National Institutes of Health (NIH)-funded basic science cardiologists. That means there are good job opportunities; if you make it all the way through the process of becoming basic science investigators, you will very likely have a good job.

Basic research is very creative; it requires that you continually think of new ways to address problems. It is also mechanistic, for those of you who have engineering backgrounds or who would like to better understand how things work. The basic science researcher will do a lot teaching. And, if you want to be a basic science investigator, there are some lifestyle considerations: scientists in this field are fairly eccentric and free thinkers. If that is you, it may give you an opportunity to do something uniquely appropriate for your personality.

How to become a basic researcher. It starts with your mentor and, today, the more mentors you have the better. If you need mentors, you might as well start at the top. Do not be shy; go talk to your chairperson. The Chief of Cardiology and the laboratory director are immediate choices. I urge individuals at our organization who are interested in doing research to form a "thesis committee" of two or three people. Touch base with these people every three to four months to go over your progress and get their advice.

In terms of choosing your immediate mentor, it is important that you find someone you like and can talk to. Many of these people will become lifelong friends and supporters. Finally, you should have what I call idols: Nobel Prize winners or other geniuses. These are the few people you look up to who you think are so brilliant you could never be that good; that sets the standard you are trying to achieve.

The second most important factor in becoming a basic researcher is the environment where you do your research. Surround yourself with the best. Find a lab that is exciting and challenging. Find a place that has trained a lot of people, because that takes a lot of expertise. Talk to the current people in the lab. Surround yourself with people who are passionate and competitive, yet friendly and collaborative, so that you can interact with them. You should feel impressed you got into that club.

In terms of the training to do basic research, it will take at least two years. There are many opportunities, such as the individual NIH National Research Service Awards (NRSA), or perhaps your institution has an institutional T32 training grant. You also can get pharmaceutical and foundation support to help pay for it. I say this sincerely: use your time wisely, and avoid the clinic. It is very tempting to help out clinically, but this is really the only time that you have dedicated to research, and you should use it wisely. I think it is critical to get publications—at least two—and to write a grant. I urge many of our fellows to write individual NRSAs or pharmaceutical grants, because it is essential for your future career to learn how to write a grant.

To accomplish all of this, you need a lot of support: financial, psychological, and scientific. In terms of financial support, you will need personal money as well as financial support for your research. Moonlighting is a reasonable way to maintain clinical proficiency, especially because you can control the amount of time you sign up for when you are moonlighting. For psychological support, talk to your friends, family, and colleagues about what you are doing. Get them to buy in, and invite them to attend your presentations. Scientific support comes from the conferences you need to attend, where you meet the experts in your field as well as your colleagues. I always tell people at the American Heart Association (AHA) and American College of Cardiology meetings to hang out at the poster sessions, because it gives you an opportunity to talk to someone one-on-one. I am very happy to talk to people who do that; it really is the most fun you can have at a conference. I am at the poster sessions to meet you.

If you want an example of how this support structure works in reality, I did moonlighting in cardiac care units and the emergency room for five years. My wife was very supportive of everything I did. She came to conferences, listened to me explain experiments, and went into labor with my son while I was doing an experiment. I had some really good friends back then who are still my friends today; I worked with them in the labs, and they were my mentors who were very supportive of what I was doing. Also, I

Table 20. How to Become a Basic Researcher: Career Paths

Fellowships
• NIH: individual NRSA, institutional training grant
• AHA: national and state fellowships
• Pharmaceutical and foundation fellowships
Junior faculty
• NIH: KO8 series
• AHA: scientist development and fellow-to-faculty
• Pharmaceutical and foundation fellowships
Next steps
• NIH: RO1
• AHA: Scientist Development Grant, Fellow-to-Faculty Award, Established Investigator, Grant-in-Aid (local)
• Pharmaceutical and foundation support

received a lot of support from the NIH and the AHA. Both Dr. Fuster and I have, over the years, paid back that support many times over by working for NIH and AHA, and this is a long tradition seen with many people assisted by these organizations.

The biggest mistake people make in choosing a basic science career is not taking enough time. No matter how good you are, research takes time. I always have MD and PhD students in the lab, and frequently, because they have achieved so much already, they think they can just show up for 6 h and turn out a good thesis. That never works. You have to work even harder to prove to everyone that you can succeed with both careers. There are no short cuts, only incomplete experiments. You need to schedule time. Do not feel guilty about not spending as much clinical time as your colleagues. A career exists over a very long time, but it requires just two years to get the basic science training you need; you should put at least 90% effort into those two years or you will not succeed later.

Make some decisions and set your priorities. For me, it came down to doing an angioplasty fellowship or not. Ultimately, I decided not to be an angioplasty fellow, choosing instead to get an NIH K08 award and do research as a beginning faculty member rather than another year of fellowship. At that time, that was one of the hardest choices I had to make, but looking back, I do not regret it.

We can't consider the basic elements of becoming a basic researcher without addressing enthusiasm. If you do not love it, you will not make it. Many people are very enthusiastic at the start, but they do not always end up loving it. Therefore, it is critical that you self-evaluate on a regular basis to see how much you are enjoying it. That also is part of the reason for writing a grant, because a grant reflects the fact that you have invested sufficient time in an idea that you are willing to defend it, that you are enthusiastic enough about your idea to carry through over the next several years, and that when it does not work the first time or even the ninth time, you still believe in the idea. I do allow people to quit after the tenth time, because if it does not work after the 10 times, then for sure it is not going to work.

Another part of science and enthusiasm is to be able to withstand disappointment; you are going to be wrong most of the time, because it is just impossible for all of your ideas to be correct. If you are going to be frequently wrong, you must be comfortable with the fact that you may set out on a project and find out that the project does not work, yet still be positive about your goals. The goal is not always directly obvious, and sometimes you have to circle around to get to the goal. That is the essence of creative problem solving, finding different ways to get to your goals. Consequently, today when I am writing a grant, it is always about something I really want to do. I have a lot of commitments, and the research time I have is one of the most valuable commodities in my career, so I make sure I am doing exactly what I want to do. I really enjoy being with people in the lab, and I tell them they are doing a good job. Even if the results of their research are negative or unexpected, it does not mean they did not do a good job. It is important to maintain that positive attitude and really sit down and talk with them. It is communication; it is dialog over results and ideas that make science exciting.

Career paths. We need more basic scientists, and there are different career paths to follow to become a basic researcher (Table 20). At the fellowship level, there are least six or seven places you can go to for funding, and organizations like the AHA have funneled most of their research dollars into training new investigators. They have very few grants available for established and senior investigators. The AHA also has this new fellow-to-faculty transition, which is a very critical grant mechanism. There is a similar effort by the NIH; it is an entirely separate case series of awards, K08s, K23s, K24s, and KL1; they are all dedicated to junior faculty.

Once you get through the junior faculty level, the next steps include getting your first investigator-initiated individual grant or R01, which is the biggest NIH grant. The AHA, even for very junior transitioning faculty, is willing to help with additional scientist development grants, fellow-to-faculty awards, established investigator awards, and local grants-in-aid. Finally, the "next steps" include pharmaceutical and foundation support.

It takes a lot of time to be successful in a cardiovascular research career, but the possibilities out there for basic research careers are enormous. Pretty much any disease you can think of that has a cardiovascular component is fundable from the NIH (Table 21).

Of all the elements required to become a basic researcher, focus may be the hardest. Find what you are good at, what you find easy to do, and what you enjoy. There is no extra credit for taking the hardest assignment. Let other people do what you think is difficult; they probably think what you find easy is hard for them. Pick a big area to focus on, such as hypertension, and then choose within this large subject matter those areas you want to tackle. Here is a question for you: If you are going to give a plenary lecture in five years based on your research, what would the topic be? What would you say that you achieved over the past five years? The key is to pick a good question—you do not have to know the answers and probably should not know the answers in the beginning, but at least choose a good

Table 21. Opportunities in Cardiovascular Research

- Diseases: hypertension, cardiomyopathy, transplant, atherosclerosis, stroke, restenosis, hyperlipidemia, arrhythmias, congenital heart disease, peripheral vascular disease
- Organs: heart, blood vessels, brain
- Disciplines: biochemistry, bioengineering, bioinformatics, cell biology, developmental biology, electrophysiology, genetics, genomics, integrative physiology, molecular biology, vascular biology
- Techniques: gene therapy, receptor biology, signal transduction, ion transport, stem cells, transgenic mice

question that can help you focus and define a good area of research for you.

Conclusions. When I started out, I was struggling to find my focus. My mentors were enthusiastic about different areas of research. Ultimately, blood vessels attracted my attention and I chose to work in vascular biology. Later, when I looked at the new techniques and the new areas of research, I looked into signal transduction, which was a still-evolving discipline when I was a fellow. When I started considering the opportunities for basic research in cardiac, vascular, and other areas of biology, I decided to work on signal transduction in the vasculature, and that is what I have done for the past 20 years.

Over the years, in my research, we have figured out a lot of the biochemistry that makes cells different from each other, and we really have some exciting ideas about redox-dependent events that seem to be different in normal flow, and this is fundamentally important because of nitric oxide (20,21). Nitric oxide goes to the smooth muscle cell and causes contracted smooth muscle cells to relax; it is instrumental in regulating blood pressure. Well, when I started out in this field, it was in its infancy and, at the time, it was not a hot field for investigation. As many of you know, in 1998 three gentlemen won the Nobel Prize for their discovery of nitric oxide: Ferid Murad, MD, PhD; Louis Ignarro, PhD; and Robert Furchgott, PhD. One might say, "You are in a field where there is already a bunch of Nobel laureates; isn't that a bad thing for someone looking to enter a field of basic research?" Well, that Nobel Prize became a very good thing. If you look at the amount of research in nitric oxide since 1990, it has gone up 10-fold as a consequence of the enormous interest in the work of these three individuals. This is really an important message: do not be frightened to go into a field that has really famous people in some very exciting areas, because the presence of such people makes the whole field much higher in both prominence and priority.

XIII. CHARTING A COURSE IN BASIC CARDIOVASCULAR RESEARCH

Stephen F. Valner, MD (Cell Biology and Molecular Medicine, New Jersey Medical School, Newark, New Jersey)

When I was going through internship and residency, my mentor at that time advised me to take a fellowship in basic research, then return as chief resident and pursue a career as a clinical investigator; however, for a variety of reasons, I never returned to clinical medicine. One reason was certainly related to the fact that I was fortunate enough to have been associated with several outstanding scientists, including Nobel Prize winners who influenced my career at medical school and during my fellowship training.

This is an example to point out that there are other career paths for clinically trained MDs interested in research. The pharmaceutical industry is another option for clinical investigators, and many of these doctors have been able to stay in "Big Pharma" or go to biotech and invest in their own companies. One example is Roy Vagelos, who as an MD became chairman of biochemistry at Washington University in St. Louis and then went on to head Merck; today, having left as president and chief executive officer of Merck, he still plays an active role in biotech. Another example: when I was at medical school, the chairman of medicine was Lewis Thomas, whose primary contributions were in research. After his medical training, he moved through the professorial ranks . Eventually, he became professor of pathology at New York University, then head of that department, and finally, chair of the department of medicine. From there, he moved on to become dean and eventually chancellor of Memorial Sloan-Kettering Cancer Center. This was to a great extent based on major research studies that spanned several disciplines. Thus, if you want to look to the future, there are a lot of opportunities for clinical investigators in leadership positions, not only in the pharmaceutical industry but also in academia.

Current career models. While my career path was that of a cardiologist who is exclusively a basic scientist, this model is mainly obsolete. One reason is that it is a career path with limited options. Obviously, on this career path you can become a professor, either in a basic science department or clinical department, and then become an institute director or a chair of a basic science department. It is less likely now for a basic scientist to become a dean or a chancellor, because understanding the economics of medicine is potentially paramount in running large medical schools. It is still possible to become a leader in a "Big Pharma," and many basic scientists also direct biotech companies.

Today, it is important to maintain your options as a clinician and as a cardiologist even if you want a career in basic research. This combination of skills is in great demand at academic institutions. Very few cardiologists have sufficient training and expertise in basic research to compete for National Institutes of Health (NIH) funding, run a basic laboratory, and bring new ideas from the bench to the bedside that will make a major difference in changing health care delivery. Therefore, it is important today for basic scientists to maintain their clinical skills, primarily for reasons of salary and career options. With this combination of all skill sets, a cardiologist can become chief of cardiology or chief of medicine, and still have the option of conducting basic research.

There are both pros and cons to this kind of mixed career. Beginning investigators may be worried about getting grant support. Recently, receiving grant support became more common with the doubling of the NIH budget. However, currently we are facing a serious dip in grant funding. Over my career, I have worked through vicissitudes of both relative ease and difficulty in receiving NIH funding. In addition to these drawbacks of difficulty in obtaining research support, if you spend full-time in research, your salary is likely to be less than if you were an interventional cardiologist, but there are other ways to increase your income and be competitive financially. Also, you have to be concerned about the time you must invest

in establishing your career, because basic research takes several years of fellowship training. Moreover, there is a need to consider the many hours you have to apply to research to be successful, run your research laboratory, teach, as well as honor your clinical commitment.

Having said that, there are several important features to the career path I have outlined that favor this approach. Primarily, there are benefits related to the diverse career options: maintaining an interest in patient care, teaching and directing a department, or working in industry or government. The intellectual challenge of this type of career is particularly attractive. While it is important to maintain your clinical contacts and see patients to gain the personal reward involved in their healing, there is also some repetitiveness to patient care. In contrast, in a research career, you come to your laboratory and work on major different projects with different methodologies, which change over the course of your career. For example, I started my research career using large animal models before moving into work involving murine genetic models and more bench work; for me, every year is a new learning experience. Thus, this combination of clinical work and basic research offers some major advantages in terms of maintaining intellectual curiosity.

Finally, a career path including research is very rewarding and fulfilling, not only in your personal and intellectual life, but also in terms of magnifying your contributions to health care. Whereas the physician can make a very important contribution to health care in terms of individual patients and individual families, with a career in basic research, it is possible to discover a new gene, a new protein, a new therapy that may improve the lives of countless patients.

Question and Answer

Dr. Fuster: You feel quite optimistic about careers in basic research, but you feel it has to be somewhat linked to the clinical scenario, which did not happen before. Can you expand on this?

Dr. Vatner: It gives the clinically trained investigator an important background and advantage in basic science in terms of knowing the end point of patient care while you are working with some gene, protein, or cell system. To be able to understand, ultimately, where your efforts are going to lead in terms of understanding the pathogenesis or therapy of disease is important, and I think that is why there is so much emphasis at the NIH on clinical investigators and investigators with MD backgrounds.

Dr. Fuster: Another change that has happened is the issue of the team effort. Your opinion?

Dr. Vatner: I fully support that, and that has been the track of my career. I started with a very small laboratory and built it up with four R01 grants from the NIH. Then we got our first program project about 15 years ago. We got our second program project five years ago, and now we are in the midst of applying for a third. We're recruiting very basic researchers. We have people—from the clinical investigator all the way to people working on yeast genetics—all working together, trying to find new pathways and novel therapies. So I agree with the team concept 100%.

XIV. CAREERS IN ELECTROPHYSIOLOGY RESEARCH

Douglas P. Zipes, MD, MACC (Division of Cardiology and the Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana)

Of the fundamentals required for a successful research career, perhaps the most important are motivation, drive, and perseverance. You need to be able to work long hours and continue to work despite disappointments and setbacks. But if I were to pick one key factor that predicts success, it would be drive.

Temperament is another important general requirement, and the temperament of a cardiac electrophysiologist combines the cognitive thinking of the cardiologist with the active approach of a surgeon. The clinical cardiac electrophysiologist requires great cognitive skills, because he/she must interpret very complex electrocardiography and electrophysiology (EP). Yet, our jobs are often surgical in nature, given that we implant devices and can locate an abnormal area of the heart and ablate it, thus curing the patient of their problem. For some years, I have been tempted to put a sign up over the EP lab, "We fix electrocardiograms," because we are virtually the only subspecialists in cardiology who actually cure patients of their problems. Other specialities ameliorate the problem, whether it is with a stent, thrombolytic therapy, or some other intervention, but often when you enter an EP lab with Wolff-Parkinson-White Syndrome or some other life-threatening problem amenable to EP ablation, you leave cured of that problem, which is really incredible.

The specific requirements for clinical cardiac EP are three years of internal medicine (IM) with American Board of Internal Medicine (ABIM) certification, followed by three years of cardiology with ABIM certification, and then one year of clinical cardiac EP, again with ABIM certification, although that year of clinical EP is definitely insufficient; practically, to be well trained in clinical cardiac EP takes two years. The complexities of the devices we use, combined with the various ablation approaches we must master, can't be learned in a year. The ABIM is probably not going to change that requirement, at least in the immediate future; nevertheless, the practical aspect is that two years of EP training are necessary. Once trained, you are required to maintain ABIM certification over a 10-year period, and you must renew your certification in cardiology and electrophysiology, while IM boards are optional.

EP research. Electrophysiology research requires training at an institution with a strong research track record as well as a recognized EP leader, good infrastructure support, and extramural National Institutes of Health (NIH) or other type of funding. Research is expensive and inefficient; it

requires time, space, and money to produce work that may or may not lead where you think it will. Indeed, one of the definitions of research has been "what you're doing when you don't know what you're doing." To a large degree, this is true, and we are often wrong more than we are right.

When starting off on an EP career, do a literature search of the publications produced by the mentors at the institution you are considering joining; find out what their track record is, how many publications they have had, particularly the individual with whom you would like to work, what their funding status is, and so on. Even earlier in your career track, while an IM resident, I strongly recommend you piggyback on existing EP studies in your area of interest, and the earlier you start, the better. During IM training, and particularly during your cardiology fellowship, seek out a mentor who is expert and willing to help young investigators. It is an important combination; it is not particularly effective to have a mentor who is an expert but who will not spend time with you. Then select a focused, doable project. This is critical, because too many young people want to invent the world, and that just does not work. The more narrow, the more focused, the more doable the project, the more likely you will succeed in completing it. It is important to demonstrate a successful track record, and by that I mean to complete a project, submit the abstract, write the manuscript, and submit it for publication.

I see young people who are good at one or two of these steps, but never take the project to completion, and that is a big mistake. These are obviously different skill sets; one person may be brave with new ideas, another, highly successful at the actual technical completion of a project, while a third person may be particularly suited to writing up the paper; however, to succeed as an independent investigator, you really need all of those skills.

Once you become part of a research team that operates like a well-oiled machine, then it is appropriate to have individuals who are specialized in a particular area. In one of the presidential pages I wrote during my tenure as President of the American College of Cardiology, I wrote about the need for the "interdependent investigator" as opposed to the independent investigator (22). The interdependent investigator is the researcher who excels at one task but not at others. This is the person who may not get ahead individually in academia, yet he/she can be a very important contributor. I chose that topic because so many of the complex research projects being done today require individuals with different sets of skills for their completion, but the fact remains that, to establish your credibility at the beginning of your career, you really need to take a project to completion, submit the abstract, and write the manuscript.

Also, you should plan ahead and write a fellowship application for your third year of cardiology training. The ABIM designates that third year as a research year, and during your first year of cardiology fellowship, you probably need to write a fellowship application to obtain funding for that third year. It is helpful in three ways: first, you get practice writing grants, and that helps focus your thinking on a particular project and consider its various aspects, such as the original concept, how the work will be done, how it will be completed, the pitfalls, and so on. Second, there is a great deal of prestige associated with obtaining a grant at that early level of training, and that becomes very important on your curriculum vitae as you apply for applications after your training. Third, by getting your own funding, you help the particular division you work for to free up $50,000 of funds if you get a fellowship grant. There are a number of grant sources, and those are discussed elsewhere.

As you consider your training, you should think about obtaining a master's degree in public health, science, clinical research, or some similar degree. The purpose is to give you additional training beyond what you will get at your particular medical center. Many places offer such programs, and you can learn a great deal during a master's level degree program that can be applied to clinical or basic research.

Research training is not complete without a thorough knowledge base regarding the protection of human subjects and informed consent. At my institution, I recruited a bright young interventional cardiologist who was also a basic scientist with an NIH R01 award. He was doing four to five clinical projects and running a basic laboratory, but he made some mistakes related to institutional review board (IRB) requirements for paperwork, such as keeping track of all the informed consent statements for his clinical projects. The IRB came down on him hard. No patients were in danger, but he did not follow the approved protocol. The IRB forbade him from doing any clinical studies for the next five years, and put him on probation for the succeeding five years. This extremely talented young investigator's science career was ruined by not following through with all of the necessary things that human subject investigation requires. To those wanting to do clinical research, I strongly emphasize being certain that you fully understand the knowledge base regarding protection of human subjects and assiduously adhere to protocol requirements of the IRB.

As many others have said: do not be discouraged by disappointments along the way. Rejected manuscripts, grants that are not approved, and failed projects happen to all of us. Indeed, if you have never had a manuscript rejected, you are not publishing enough. Even at our senior level, we still get manuscripts rejected from prestigious journals. You pick yourself up and resubmit the manuscript someplace else. Rejection is difficult from an emotional and ego standpoint. When you write something and submit it, you're putting your ego on your sleeve, and when you receive criticism, initially it is very difficult to press on, but you need to pick yourself up and continue.

My 40-year research career has been spent with one foot in the animal lab and one foot at the bedside. When I first transitioned from my cardiology training and had the opportunity to spend a sabbatical doing basic science, one of the things that struck me within the first few weeks of doing basic science was that you can go a very long time without

any positive feedback. Think for a moment about your clinical experience. Virtually every day, some patient got better and thanked you for the care you gave. In the clinical setting, you receive positive input daily, and we thrive on that; however, in a basic laboratory, you do not have that kind of feedback. Indeed, if your experiments are not working, you can go weeks or months without any positive feedback. After the first six to eight weeks, I was depressed and I could not figure out why; then I realized it was because I went from being a clinician to a basic scientist, and with nothing succeeding in the research I was doing, I had no positive feedback for quite sometime. You really need to be aware of that going in and understand the nature of basic science work as opposed to clinical work, where positive feedback is a daily occurrence.

However, I cannot adequately express the thrill you get when you conceive a hypothesis, go to the bedside or the basic lab, and prove that what you conceived is correct. For that small moment in time, you may be the only person in the world who possesses that knowledge, and there is nothing that I have found that exceeds that, intellectually. For me, that is one of the driving forces that have made me so excited about research for 40 years. The thrill of that discovery is what creates the fire in the belly.

Basic cardiac EP. For basic cardiac EP, the ABIM offers an investigator track. This shortens the IM program by a year. After two years of IM training, the ABIM investigator track requires three years of research, which can be molecular biology work, patch clamping/mapping, or clinical research. Then it is on to two years of clinical cardiology and one year of clinical EP, should you choose to become both a clinician and a basic scientist. Once again, careful selection of the mentor and the project is very important; keep it focused and make certain that the project you have chosen to focus on is something you can accomplish in the time you have allotted.

At the junior staff position, make sure you "get it in writing" the recruitment promises. This includes a clear understanding of your protected time. The amount of protected time you get will depend on what you want to do, but at a basic level, you need far more protected time for basic science research than you would if were going to be a clinical investigator. You also should get in writing the research support you will need for a minimum of two years, including technician, lab, expenses, and salary. Finally, have an agreement giving you the opportunity to take classes in statistics or other pertinent areas. At this point in your career, focus, publish, and get grant support.

Can you be a clinician and an investigator? For clinical investigation, certainly, it is no problem to be both, but the combination is much more challenging for basic investigators. When I started, it was relatively easy to be a basic electrophysiologist and a clinical electrophysiologist, so I just grew up that way. Early in my career, the chairman of medicine related to me the story of a young farm boy who was given a calf. Each day he lifted that calf and, despite the fact that the calf grew to be a big cow, since he started lifting the animal when it was still small, he was able to continue lifting the animal when it grew well beyond calf size. That is how I managed to start at the basic science level, and even as it grew more complex, I was still able to do it. Today, that approach would be much more difficult. It is not impossible; it is doable if you work hard. Particularly helpful is choosing a project that addresses a clinical question (i.e., translational research). In our labs, the thrill has been the bidirectionality of the research we do. If we have a clinical question that cannot be answered readily at the bedside or in the EP lab, we bring it to the animal laboratory and get an answer. Conversely, we can take a basic idea and translate it to the clinical area.

The "C" in implantable cardioverter-defibrillator, or ICD, was developed by taking a concept from the animal lab (23) and bringing it to the clinical area (24); we do the reverse as well. We had a series of studies recently, using optical mapping in an animal model to explain the mecha-

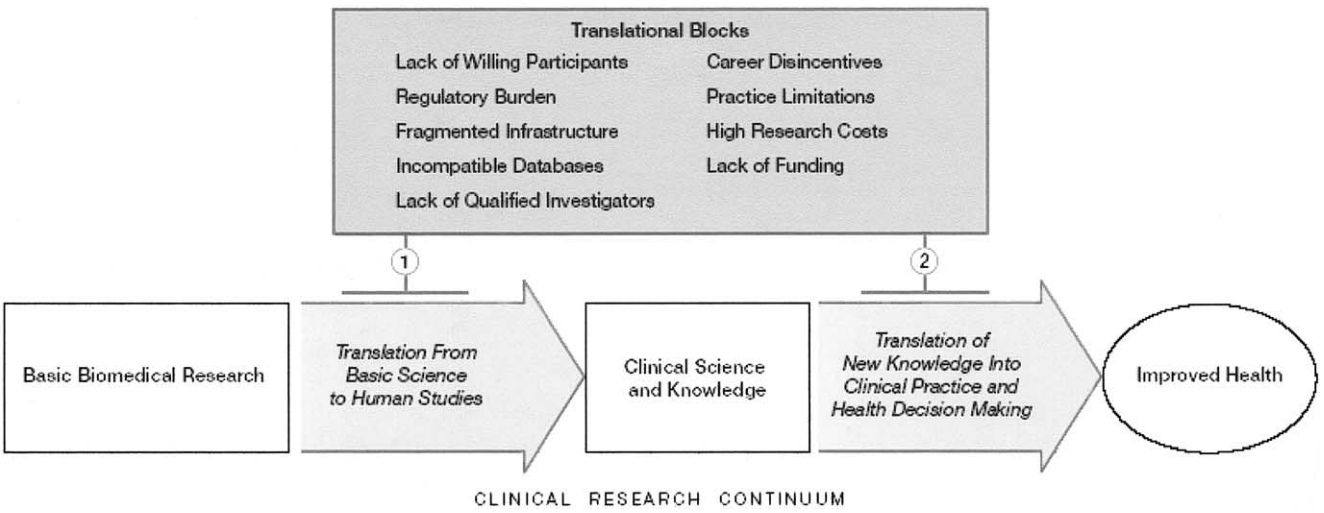

Figure 7. Traditional paradigm. Source: JAMA 2003;289:1278–7. Copyright ©2005 American Medical Association. All rights reserved.

nisms of ventricular tachycardia and atrioventricular node re-entry that we see clinically (25–27).

It is also important to pay attention to patentable ideas. When we implanted the first cardioverter (24), it drew interest from the news media, including having a news conference. After the news conference, my dean threatened to fire me if I ever did anything like that again, but today most schools want that kind of publicity. They want you to patent ideas, because it raises money that helps support other kinds of research. So, intellectual property is very important to both you and your university; clearly, one should take advantage of ideas that can be patented.

Conclusions. The EP job market has never been better, especially for those with a proven research track record demonstrating the ability to take a project from concept through protocol writing, IRB approval, data collection, analysis, presentation, and publication. Electrophysiologists are in great demand; for instance, ICD implants are growing at a rate of more that 20% per year. We now have biventricular pacing that we can combine with ICD technology; indeed, some 40% of that growth in ICD implantation is in units that include biventricular pacing, so the market is increasing dramatically. Atrial fibrillation and sudden cardiac death remain major problems and will continue to provide job security for the basic and clinical electrophysiologist well into the next century.

Considering the striking advances in both our understanding and treatment of cardiac arrhythmias (28) and the explosive growth in EP, there it is certainly a wonderful job market for the individual who fits the picture I have described of the EP researcher.

XV. MAKING THE TRANSITION TO TRANSLATIONAL INVASIVE RESEARCH

David R. Holmes, Jr, MD, FACC (Mayo Clinic College of Medicine, Rochester, Minnesota)

There are many different ways to define translational research. Translational research integrates science discoveries into clinical applications or, conversely, uses clinical observations to generate research foci for basic sciences. It is designing strategies to test basic pathobiologic or pathophysiologic concepts of disease in a human/clinical arena. It is also identifying mechanisms of disease or healing in individual patients that can then be tested in larger, validated population studies. Or it can identify patient populations with disease and then study the cellular mechanisms of the disease or that particular population. These are all examples of translational research and how it relates to interventional cardiology.

In a recent article on the central challenges facing national clinical research, the authors described the first roadblock as translating information from concept into first human studies, and the second roadblock is the translation of information from clinical trials into clinical practice (Fig. 7) (29). Invasive interventional cardiologists may find they have interest in both of those roadblocks and involve themselves in trying to get that information from science to a specific patient or to the larger population.

Historical perspective. In a 1997 article in the *Journal of Clinical Investigation*, Goldstein and Brown (30) tell the story that pinpoints the modern beginnings of translational research. Philip Hench (1896 to 1965) (31), a rheumatologist at the Mayo Clinic, noted in 1929 that several of his patients with painful rheumatoid arthritis experienced dramatic improvement if they were either pregnant or jaundiced. He hypothesized that these conditions produce an anti-inflammatory hormone he called "anti-rheumatic substance X."

The only common biochemical denominator he could find in pregnancy and jaundice was elevated cholesterol, so he administered lipid extract from bovine adrenal glands, but no antirheumatic effect was seen.

Five years later, he began collaboration with Edward Kendall, PhD (1886 to 1972), a chemist who had already isolated cortin, a crystalline substance composed of 28 different steroids, from the adrenal cortex in dogs. Kendall was able to isolate six steroids with activity using bioassays. Working together, the men tried to identify and purify the six steroids showing activity. Separating closely related steroids was an arduous process that required 10 years and 150 tons of adrenal glands. Their first study involved compound A, which was 11-deoxycorticosterone, but it failed. They moved on to the sixth steroid, which was cortisone.

Finally, in 1948, after starting in 1929, Kendall and Hench, in collaboration with Merck and Co. Inc., devised a 37-step process for the synthesis of cortisone, the most elaborate biochemical method process created to date. They produced several grams of cortisone, enough to treat one rheumatoid arthritis patient with 100 mg intramuscularly for nine days. In a video shown in 1949, a dramatic effect was obvious in a 61-year-old patient with chronic, severe rheumatoid arthritis who couldn't even walk before the treatment. The Lazarus results in an immobilized patient is an example of translational research and led, the next year, to the two researchers sharing the Nobel Prize in physiology or medicine.

This is translational research. It worked because it was based on clinical observation, clinical need, and collaboration between a passionately committed clinician, a basic scientist, and a pharmaceutical company. Success required confidence and resolution despite repeated failures. It required innovation and resources and is pretty much where translational research emerged as a field, where those same concepts apply as much today as they did then.

Making the transition. Clinical observation, clinical collaboration, confidence, resolution, innovation, and resources are all common themes in translational research. How, then, do we make the transition to interventional translational research careers?

If you are an interventional cardiologist and would like to

be a translationalist, you will need formal scientific training with mentors, and it will require rigorous and focused training based on whether you decide to concentrate on cellular, biochemical, or molecular research, or perhaps some combination. Because of the emphasis on basic science, your formal scientific mentor is unlikely to be an interventional cardiologist, but the mentor should have had advanced clinical interventional practice who can identify issues and be aware of the technology. This will perhaps require a couple different mentors.

Once mentorship is in place, with both basic science and interventional experience, the next crucial ingredient is translational research space and equipment, access to an animal laboratory, and relevant state-of-the-art equipment to assist in studying those ideas brought along from your basic science training and then carrying the findings into the human arena, which means some facility for patients.

There are other considerations, too, as the work progresses, including a mechanism for intellectual property development and protection, since you will bring along new technology and want to protect and develop it. A research support infrastructure is necessary for protocol design and development with Food and Drug Administration interaction. Funding mechanisms will be necessary as well as internal or external facilities for prototype development. If you have a specific widget in mind, you have to have a prototype of that widget to test in the animal laboratory.

Career issues. In translational invasive research, there a number of career issues. Who are your peers? It may be the interventionalist who does percutaneous coronary intervention, or perhaps the basic scientist, or it may, in fact, be people somewhere in between with feet in both camps.

One key issue is figuring out what you are going to do with your interventional practice. Suppose in your interventional training you did 500 interventions, but now you have NIH funding requiring 70% of your career be devoted to the NIH-funded project. You certainly will not be doing 500 interventions or even 200 interventions. It may be possible to do a handful of interventions, but what does that mean? How will you manage your clinical commitments? An interventional cardiologist must devote time to interventions; otherwise, that skill goes away. These decisions will have to be made, and they are likely to be difficult.

When doing device or drug research, protocol design issues include whether you are going to use highly selected or real-world patients. Does the situation call for a randomized trial, a registry, or a Humanitarian Device Exemption?

Finally, consider conflicts of interest: who will design the protocols and, if it is your device, who will use the device? Should it be you? Who will report the data? Who benefits from financial gain? Hopefully, that concern will be an issue because your device and career will be successful.

Real-world examples. With that background, consider these three different approaches to becoming an invasive interventionalist/translationalist cardiologist, all based on real people.

The first example did his interventional cardiology training at the Mayo Clinic. At Mayo, he did 434 interventions and published nine papers in interventional cardiology. We discussed what he was going to do when he grew up, and he decided to take the road less traveled, eventually going into gene therapy research. Today, he has three patents and does zero interventions, is a star in the field of gene therapy. His trip took him from interventional cardiology into basic molecular mechanisms, where he decided to stay and design treatment strategies for small discreet patient groups.

The second person is on more of a "mainline highway." After internal medicine residency at Mayo, he stayed as a cardiovascular fellow, which included two years as an NIH research fellow within the fellowship. In 1997, he was the Director of the Center for Coronary Physiology and Imaging in the catheterization lab and a professor of medicine in 2001. His major research interest is human endothelial dysfunction, which has led to a randomized trial on L-arginine and endothelial dysfunction and a subsequent NIH R01 grant to study endothelin in early atherosclerosis.

Finally, the third example is a colleague originally from Ireland, who started out as a PhD in vascular biology. He came to the Mayo Clinic as an interventional cardiologist, where he did 370 interventions. He became a postdoctoral fellow and is now an assistant professor of molecular pharmacology and experimental therapeutics. In 2004, he did no interventions; instead, he has an Australian National Heart Foundation Research Scholarship, an AHA [American Heart Association] beginning grant-in-aid, an NIH PPG and R01, and developed a wound care technology for which he received a $2.5 million grant from the Department of Defense/Homeland Security. Additionally, he is the principal investigator planning a phase I clinical trial of genetically modified stents for chronic total occlusion.

Conclusions. Obviously, you can get to translational invasive research in different ways. If you arrive there as an interventional cardiologist, you will have to decide whether you want to stay as an interventional cardiologist who communicates with the basic scientists for the cross-fertilization that is necessary for success. This approach can be extremely productive and make for great success, all achieved from the platform of interventional cardiology. The value is due, in part, to the fact that there is a large data set of patients in an interventional practice, providing an enormous amount of information that can help advance the care and treatment of these patients.

XVI. PANEL DISCUSSION: MOVING BEYOND THE CLINICAL EXPERIENCE—SPECIALIZED RESEARCH OPPORTUNITIES: PART 2

Robert O. Bonow, MD, FACC (Northwestern University Feinberg School of Medicine, Division of Cardiology, Northwestern Memorial Hospital, Chicago, Illinois)

Valentin Fuster, MD, PhD, FACC (Zena and Michael A. Wiener Cardiovascular Insitute and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center, New York, New York)
Douglas P. Zipes, MD, MACC (Division of Cardiology and the Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana)
David R. Holmes, Jr, MD, FACC (Mayo Clinic College of Medicine, Rochester, Minnesota)
Bradford C. Berk, MD, PhD, FACC (Center for Cardiovascular Research, University of Rochester Medical Center, Rochester, New York)

Dr. Fuster: We have heard a lot of discussion on the importance of the team in research. What is your gut feeling about working together on a team, regardless of the field that you are in?

Dr. Bonow: A multidisciplinary approach is critical in the development of research topics, and that is even true within cardiology. I do not care whether you are going into electrophysiology, intervention, or whatever; my recommendation is the same: use multidisciplinary teams. We really see a trend for the future in being able to get good engineers, chemists, and molecular biologists to all team up to solve a given problem. What I find to be utopian is when you can have people with a variety of interests, such as individuals interested in atherosclerosis, others working on electrophysiology problems, and still others interested in interventional aspects, all working together and melding those diverse interests into some common questions and solutions.

Dr. Fuster: The question is stimulation and incentive. Somebody raised the issue that today you can go to a private or semi-private organization and have more money for research and still accomplish many things. Please respond to that, because my concern is that while you may go to these places to do very specific work and the money may be there, I am not entirely sure you have the team, the stimulation, or the excitement.

Dr. Bonow: I agree with you. Often in these environments, the reason you get the money is because of the highly focused effort. Secondly, it is very difficult in those circumstances to develop the type of multidisciplinary team I just outlined. There are exceptions to that rule, obviously, but in general, it is very difficult to end up generating that type of interdisciplinary team when the funding structure is so narrow with regards to the outcomes that have to occur.

There is a huge temptation to move in that direction, and it is something younger cardiologists are going to be faced with more and more when making career decisions. It comes down to basic research versus more applied research; if you want to do basic research, these types of multidisciplinary groups with the more classical academic environments are going to be required. If you lean more towards applied research, such as the phase III trials, the private group or institute approach might be tenable. It really depends where your talents and interests lie in terms of what model you follow.

Dr. Fuster: Let us say I am an electrophysiologist and I move into some kind of private setting. I still do research, but would not it be very important to keep in touch with the university setting and with all the groups who are really skillful?

Dr. Zipes: There are two parts to this issue. One is your multidisciplinary team, your ability to garner the technology and disciplines necessary to really ask the question and probe for an answer. As I said, imaging is a huge part of what we do as cardiologists, and being in a place where you can look at what you are studying is critical. There are many different ways you need to look, all the way from good old-fashioned autopsy pathology to real-time imaging using CT and MR technologies. Those images give you some tangible mechanism to understand what you are studying, and it is incredibly important that in all these areas of investigation you have that ability to look at what it is you want to study. That is, sort of, a technology side.

The other half of the equation, which is even more important, is the intellectual environment you are in. You can be hurt if you end up in a place that is so narrow that all discussions are limited to a single topic or a single body of investigation. It is essential to be where people are asking a lot of good questions, where there is a lot of intellectual fervor about the whole field, because it is that cross-fertilization that is so important. This is so important that I had one big complaint about the last American Heart Association Scientific Sessions; the biggest problem we had was we were so spread out throughout the convention center that it was very difficult for the basic scientists to mingle with the clinicians and the epidemiologists. I hope that the program committee modifies this, because it is that mingling that is so essential for good ideas to emerge.

Dr. Fuster: David, you have been a good example of staying focused yet occasionally peeking here and there into other fields within a multidisciplinary environment. Please explain how to do this.

Dr. Holmes: You can choose a highly specific area that is continuing to evolve and grow, and through this growth, multiple disciplines may all come to bear on that very specific area: multiple people from different walks of life will ask different questions, and all have different answers to the same questions. That is a very important point. Sometimes we ask a question, thinking that we know the answer, but then somebody interprets the question entirely differently and gets a very different answer.

There is another issue that has not been addressed very well, at least, as we consider cross-fertilization and perhaps imaging. In many institutions, there are silos. These need to be broken down; cross-fertilization is necessary between silos and outside the silos. As an example: I am learning carotid stenting from a neurosurgeon in Buffalo, New York; the reason why is because we each ask different questions

than each other, and together, this combination is very powerful. So, in learning this, I may see things differently, which gives further strength to our collaboration.

As you begin to look at career opportunities, think about the silos that are within whatever institution you are going to work at. There are institutions where Radiology says, "You cannot do MRI [magnetic resonance imaging]. You cannot do CT [computed tomography]." Consequently, one of the requirements for considering tremendous career advancement is that you go to a place where the mechanics of cross-fertilization already are in place or there is a willingness to break down silos.

Dr. Fuster: One of the critical issues we talked about was generosity, giving something to the other person and the other person giving to you. If you are stuck in your field and are defensive, forget it; there are no silos that are going to be broken. That is the reality of the world we live in today.

Dr. Holmes: This is the first time I had seen a slide that listed altruism as being an element of a good scientist. One way you break down silos is by not necessarily having the vested interest that keeps us from collaborating, and they may indeed require a bit of altruism as well. I applaud that attribute in successful scientists.

In terms of what you said about broad interactions, at our institution, our research conferences are attended by basic scientists and clinicians to provide cross-fertilization. And at a global level, the clinician is able to help the basic scientist ask the questions that are important from a clinical standpoint, and the basic scientist is often able to critique the clinicians and make certain that they stay on line in terms of their focused research. So, that kind of interaction is absolutely essential.

Question: I have some interest in genomics and their relation to electrophysiology. As someone who would like to do more translational research in terms of populations, I want to know whether a PhD is something [that] would be required for that kind of work.

Dr. Holmes: At our institution, we have a number of MDs who essentially function as PhDs. So, I do not know that it is the title, per se, as much as what the knowledge represents, and to me, the latter is more important. I do not think you need to be holding a PhD necessarily, as long as you have had the two to three years in a basic lab acquiring the skills to do the kind of genomic research that you would like to do.

Question: I ask this question as someone admittedly lacking a little bit of focus, because of my interest in imaging and ethics in cardiology. It seems to me that, in the absence of good National Institutes of Health (NIH) funding, someone is fairly dependent on industry when you are involved in the use of new technologies. How do you negotiate with industry when they seem so indispensable in a lot of research settings?

Dr. Berk: Some aspects of cardiovascular research have an applied industry focus. The good news is that if they want you, then you certainly can get them to agree to a contract and to provide you with a funding and you can hold them to those contracts. It is true that the NIH is a much safer bureaucracy than most industries, which experience constant changes in their business plans and personnel. The National Heart, Lung, and Blood Institute as well as the other NIH institutes have been around for more than 50 years and are very stable environments. I think all of us make our primary focus to obtain NIH funding, but that said, a very focused appeal to industry to do something that is of mutual benefit usually ends up being quite successful.

Dr. Holmes: In terms of your relationship and negotiating with industry, one important point is to negotiate up front some of the rights to the data. I am going to give you a concrete example. I was the principal investigator for the PRESTO (Prevention of RESstenosis with Tranilast and its Outcomes) trial. This was the largest trial of interventional cardiology for restenosis, and several years ago we thought the results were going to be incredibly positive. While the study was being planned, we asked the sponsor to fund a publication center and 20 manuscripts, any 20 manuscripts that we wanted. We wanted them to commit those funds up front, and they agreed.

It turned out that the trial was negative. But we had in place the ability to continue working with this 10,500-patient data set and to write what ended up being good population studies. Subsequently, we have published 20 papers out of a negative study. Had we not negotiated that up front, the drug company at the end of a negative trial sometimes just disappears as does everybody associated with that trial.

Dr. Zipes: There is yet another aspect to working with industry; you can have a great scientific idea, but if it can't find its way into the market place because of regulatory issues, that can be a major stumbling block.

Question: I have two questions about career planning. First, I would like to understand why someone would want to be become a department head or chief of medicine or some comparable post, because it looks to me like it steals part of your time. The second question pertains to the future of interventional cardiology. We see so many advances, and maybe one day we are going to have a drug that melts plaque and 80% of the interventionalists are going to be out of business. How do you see the future of interventional cardiology?

Dr. Fuster: Though it is true that everybody sitting on this panel is the head of something, I do not think this is necessary for everyone. When you really work in research, we have so many people who are not necessarily heads of anything. Moreover, probably 75% of the ones who are department heads are not really the mentors who are going to make your research careers interesting. You should not take away the impression that you have to be the head of anything.

Dr. Zipes: Becoming head of cardiology was not the most important contribution to my own career; I never considered it until shortly before I assumed the position. In fact, it was

more of a defensive maneuver in my own institution; I did not want someone else to be head of cardiology. I once plotted the number of manuscripts per year in my career and they fell dramatically when I became head of cardiology. So for those people who are seriously interested in a research career, my bias is to do the research and not get involved with administrative responsibilities, except for your own survival. You may need to have some sort of a power base to be able to determine what it is you would like to do.

Dr. Holmes: That is true, although I would add that if your career is based upon developing strategies, or taking care of groups of patients, or doing population research, then sometimes you are in a very good position as an administrative head to hire the people necessary to make that happen and to carry forward your vision.

Dr. Zipes: Besides payback for the successes of a career, an administrative post may help you put policies into place that you have developed and would now like to take control and move in that direction. Also, some of the best chiefs I have ever interacted with are those who really have a love for the institution and a love for the science and they want to see both propagate.

As for your other question, as to whether we are going to put any field of science out of business by curing cardiovascular disease, I do not think there is a need to worry about that just yet.

Question: My question pertains to Dr. Holmes' talk on the invasive cardiovascular translational scientist. The examples you presented are very interesting, and we can aspire to be like the people you discussed. Obviously, it takes a lot of hard work, dedication, and time. I have a PhD in cellular molecular biology, went through internal medicine, chief residency, a cardiovascular fellowship, and am in my third year applying for interventional cardiology. Do you feel that it is essential to have that one year of interventional cardiology training? The people you spoke of probably had that interest and drive to do those procedures and go into interventional cardiology, but they are doing zero procedures today. Was that year essential to get where they are now or to get the focused projects that they need?

Dr. Holmes: That is a great question, and I think the answer is yes, it is important to put in that year. It is important to be immersed in the clinical arena for a certain period of time, to know the problems that are faced by the patients or in terms of the system itself, to know what it feels like, then actually having been there is essential. All of those individuals would agree. They were interested in making those relationships, and that was part of that process; being side-by-side, facing the same sweaty issues. Once you have that relationship, you can move ahead and build on those relationships, and they have done that. All of them would say it was a tremendous year, not a wasted year. They picked up the currency of the field.

Dr. Zipes: Our interventional cardiologists are the most sought-after collaborators within our program right now. Their skills, their knowledge, their appreciation of the problems as well as their ability to attack the problems in innovative fashion are very important elements in our research team. I am glad they took the year to get interventional training and I am glad that they are in our institution.

Question: How much basic science research do you need to know to become a clinical investigator, and if you do not have much basic science training, how do you go about getting it? Also, if you are in an institution that does not provide a good infrastructure for clinical or basic research, how do you pursue a career as a clinical investigator or in academic cardiology?

Dr. Fuster: In regards to how much basic science you need to become a translational researcher; all I can say is you certainly need it. I have a PhD and spent three years in getting it, but if I had to start again, I probably should have studied basic science at least for one or two years. I got into a field that was evolving, and I have been able to carry through successfully with NIH, but this is getting tougher.

In terms of your institution, if you are not in the right environment, move out. Only you can decide what you want; if what you want is to succeed in an academic career, you will become a neurotic wreck staying in a place that doesn't provide what you know you need and want. It may take time to find the right place, but that is what I would do.

Question: I am starting my interventional fellowship next year. How do I go about continuing my career in interventional cardiology and then move on to the field I am interested in? Unfortunately, my institution does not have much in the way of research in this particular field.

Dr. Fuster: That is a rather complex question, and I say go with your gut feelings. You have to get down to earth and ask, "What am I going to be contributing to, and where is the best place to make that contribution?" Be very practical and allow yourself to guide you in one direction or the other.

Dr. Bonow: You have heard how important environment is and how important actions are. If you are not in the right environment, then the advice from Dr. Fuster is correct. That gut instinct, as he called it, would be the indication that you have the fire in the belly to do research and you have great curiosity about problems you can solve. It might be that you need to look at the institution.

Dr. Fuster: We are not suggesting making a hasty decision. Many times we become impatient because we want to achieve everything rapidly. Give it time, be patient, and go step by step.

Question: It is clear that you have to have the fire in the belly and that in any academic career you must be committed and dedicated over the long term. But what about the other fires that we may have, such as the fires we may feel for teaching or getting involved at the bedside?

Dr. Fuster: While we are discussing academic approaches to life, we also are talking genetically. Whatever the fire is, just follow it and find out who you are.

Dr. Holmes: There are many different sorts of fires. You can find incredible rewards in a lot of different areas in cardiovascular disease. For instance, you might say my

ability to interact with scientists is really fun, but what I really want to do is to look at population approaches to disease. Therefore, perhaps you get involved in something that is incredibly valuable to the practice of medical care, such as the American College of Cardiology Guidelines Applied in Practice Program. If that is what you would like to do, there is tremendous opportunity to do that, but only you can decide what it is that lights your fire.

Dr. Zipes: I want to speak to family issues, which are critical. Do not sacrifice your family for your career. If you miss your 7-year-old son's birthday, you can never make it up and he never forgets it. Spend time with the family. Coach Little League. Do all the things that are important, because when you get the gray hair that we have and have done your research, one of the most important factors in your life is your family; do not become estranged from your wife and children. At times, you need to stay in the lab with an experiment that is working and you may get home late for dinner, but in the main, make the decisions that are important for the family. Family comes first!

Dr. Berk: I totally agree. As I said in my presentation: involve your family, take your kids to the labs, take your wife to the meetings, let them know what it is you are doing so that they are part of that. If you are happy and you come home happy and excited, they are going to naturally want you to be that way, so the more they understand, the happier they will be. That said, there is always this ambivalence of, "Do I agree to write one more paper, chair one session, go to one more meeting, show up Saturday morning in Washington to talk to all of you?"

But some of these issues—I call it ambivalence—are unresolvable. To be successful, you have to learn to live with the fact that you are never going to resolve this, and it is always going to be an issue. If you recognize that fact, then at least when you get up every morning, you are cognizant that "I am going to have to deal with it and do it successfully." Then most people figure out good mechanisms to do that.

Dr. Zipes: One approach that worked for me was I did all of my writing at home. Obviously, you do the experiments or whatever in the lab and at the hospital, but after dinner and the weekends, where it was just the writing of the paper, I did all of that at home. That way, my wife and children always saw me there and I could take a break and go out and throw a ball with the kids or whatever.

Question: There is no doubt in my mind that most of us will have a career change. How do chairs of cardiology look to junior faculty when they make a career change, and what fatal mistakes would you advise us to avoid if we are making a career change?

Dr. Berk: Do not make it in isolation. If you are feeling that some aspect of your career is not very satisfying right now, you need to communicate that to your chief. Part of a good chief's role is to mentor you, point out your talents, talk about what is not satisfying in your current career, and help guide you towards a better career. As chiefs, we invest a lot of time in our fellows and in our junior faculty. You are the currency that we are judged on, and if I have invested a lot of my time and energy in a junior faculty member, I want that person to succeed.

When people are making career changes, that frequently is the time they need to acquire new skills. It is the chief's job to help them choose where they are going to get the skills and to know whether our institution is the place to do that.

XVII. CARDIOVASCULAR GENETICS, GENOMICS, AND PROTEOMICS: CAREER OPPORTUNITIES ABOUND

Christine E. Seidman, MD (Harvard Medical School and the Cardiovascular Genetics Service, Brigham and Women's Hospital, Boston, Massachusetts)

The application of genetic, genomic, and proteomic approaches to discover cause, understand pathophysiology, and ultimately to treat cardiovascular diseases has garnered considerable excitement among physician-scientists. The opportunities to participate in these novel investigative methodologies are many, whether as a research leader or as an academic practitioner. Molecular genetics and genomics is particularly rewarding for physician-scientists, because these disciplines require clinical skills and insights as well as basic research methodologies. For me, these fields of investigation satisfy both a desire to participate in creative discovery and real opportunity to practice medicine. If the considerable technical advances in genetic, genomic, and proteomic platforms are going to realize their full potential for creating powerful new tools in modern medicine, clinician-scientists must contribute to interdisciplinary teams that will transform biomedical potentials into clinical realities. Some medical disciplines appear more proactive in assembling the interactive teams needed to harness these methodologies to solve human disease. For example, the rich collaborations between oncologists and cancer researchers have promoted a remarkably rapid pace in the discovery of the molecular causes of malignancies, in the definition of early serologic markers of disease, and in the identification of signatures associated with aggresive cancer properties, work that has fueled the design of novel rationale therapeutics. These same opportunities exist throughout cardiology to foster a better understanding of the causes and cures of heart disease.

In the context of my research laboratory, we use genetics, genomics, and transcriptional proteomics to discover the molecular causes of cardiovascular disease, and use this information to build models appropriate for deciphering disease mechanisms and for defining potential therapeutic targets. This work integrates colleagues who are trained in a variety of different career paths including clinical cardiology, population science, molecular and cell biology, and bioinformatics. Therefore, the "lab" is a virtual place that includes clinical, computational, and wet-bench space.

Molecular genetic investigation of cardiovascular disease

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Table 22. "Solved" Monogenic Cardiovascular Disease: Metabolic/Vascular Disorders, Cardiomyopathies

	Gene Locus	Gene Product
Metabolic disorders		
LDL	2p23	apolipoprotein B
LDL	19p13.2	LDL receptor
HDL	11q23	apolipoprotein A-1
Lp (a)	6q26	Lp (a) lipoprotein
Homcystinuria	21q22.3	cystathionine b-synthase
Hemochromatosis	6p21.3	HLA-H
Amyloidosis	18q11.2	Transthyretin
Vascular disorders		
Marfan syndrome	15q21	Fibrillin
Ehler-Danlos IV	2q24.3-q31	Type III collagen
Supravalvular aortic stenosis	7q11.2	Elastin
Osler Weber Rendu (HTT)	9q	Endoglin
Coronary disease	15q	MEF2A
Cardiomyopathies		
Hypertrophic	1q3	Cardiac troponin T
	11p13-q13	Myosin binding protein-C
	14q12	Cardiac b myosin
	15q2	a tropomyosin
	15	Cardiac actin
	3, 12	Regulatory light chains
	2q24	Titin
Glycogen	7	PKAG2
	X	LAMP2
Dilated	15q14	Cardiac actin
	14q12	Cardiac b myosin
	1q32	Cardiac troponin T
	2q24	Titin
	6q22	Phospholamban
	12p12	ABCC9
Dilated/conduction system disease	1q21	Lamin A/C
	3q25	?
Barth's syndrome	X	Tazaffin
Duchenne muscular dystrophy	Xp21	Dystrophin
Friedereich's ataxia	9q	Frataxin

began over 20 years ago with the study of single-gene defects. My research in this arena was spurred by a long-standing clinical interest in cardiac remodeling; faced with any one of a myriad of different adverse stimuli, the myocardium changed in one of two distinct patterns, becoming hypertrophied or dilated. Although the clinical and histopathologic manifestations of either remodeling pathways were well described, clues about the molecular and cellular processes that triggered cardiac hypertrophy or dilation were few. Human molecular genetic study of familial or inherited forms of cardiac remodeling provided a powerful new approach to discover the pathogenetic mechanisms that caused cardiac remodeling. My laboratory undertook clinical evaluations of families with inherited cardiac pathologies, assessed the mode of disease transmission, and used molecular genetic analyses to determine the chromosome location of disease genes and ultimately defined disease-causing mutations. This approach, sometimes termed reverse genetics, while initially focused on heritable heart disease in families, is also the fundamental principle on which the discovery of genes that contribute to heart disease in the general population is based.

The power of genetics and genomics comes from the unbiased approach in which the entire human genome is analyzed. With the development of extensive libraries of single nucleotide polymorphism (SNPs) or non-functional deoxyribonucleic acid (DNA) variants that are scattered throughout the human genome, genes that cause or contribute to cardiovascular pathology can be precisely located on a particular chromosome region. This genomic mapping provides information that directs subsequent analyses to molecules encoded within the region with biologic relevance to the disease. Furthermore, the incredible wealth of information about gene expression and function in the hearts of many model organisms as well as in humans provides considerable information for interrogating the relevance of potential candidate genes in cardiovascular pathology. Taken together, datasets that allow genomic mapping of disease and annotated gene information have considerably accelerated the pace of cardiovascular disease gene discovery.

Monogenic cardiovascular disease. Human genomic research efforts has changed a once bland map of the human genome into one that today is littered with annotation of

Table 23. "Solved" Monogenic Cardiovascular Disease: Arrhythmias and Congenital Disorders

	Gene Locus	Gene Product
Arrhythmias		
Prolonged QT syndrome	3p21-24	SCN5A
	7q35-36	HERG-K+ channel
	11p15.5	KVLQT1
Brugada's syndrome	3p21-24	SCN5A
Lev's disorder	3p21-24	SCN5A
Familial heart block	19q13	?
Congenital sinus node dysfunction	4p	
Atrial fibrillation	1	
ARVD	1q31	Plakophilin
	17q21	Plakoglobin
	6p24	Desmoplakin
Exercise-induced VT	2	Ryanodine receptor
Congenital disorders		
Velocardiofacial syndrome	22q11.21-q11.2	TBX1
Holt-Oram syndrome	12q2	TBX5
ASD with AV block	5q35	Nkx2.5
ASD/atrial aneurysm	5p	
ASD		GATA4
Carney's syndrome	17q23	cAMP-dependent protein kinase

disease genes for virtually every type of cardiovascular pathology (Table 22). Our appreciation of the role of genes in lipid and cholesterol metabolism has been greatly expanded and enriched since the early discoveries of mutations in the gene encoding the lipoprotein receptor. Other systemic disorders including hypertension and diabetes that enormously increase the risk for heart disease can also arise from single-gene mutations. Primary disorders of the heart, hypertrophic and dilated cardiomyopathies, and cardiac electrophysiologic disorders can arise from inherited gene muations. Discovery of the genetic contributions to structural malformations affecting the vasculature, including both the great vessels and the microvasculature and congenital heart malformations are increasingly identified.

In addition to providing new and fundamental biologic information about specific diseases, knowledge of the molecular basis of these diseases has also changed the way in which we clinically evaluate and manage disease in patients. For example, given a genetic substrate for cardiovascular disease, the clinician must look beyond an individual patient to all first-degree family members who are at risk for developing the disease. While families are often aware of increased risk because of familial relationships, health care systems have yet to incorporate appropriate mechanisms to counsel and evaluate family members. Similarly, the individual with genetic risk for cardiovascular disease but without overt disease manifestation poses another new challenge for the new field of cardiovascular genetics. These individuals define a new and preclinical phase of cardiovascular pathology—when traditional signs and symptoms are subtle or absent. Detailed assessment of cardiovascular morphology and hemodynamics that characterize this phase may uncover new clues about disease initiation and may indicate factors that stimulate conversion from genetic risk of genetic disease. Insight into this earliest disease phase provides enormous opportunity for interventions that may prolong disease-free duration or attenuate cardiovascular disease expression. Clinical investigations that harness novel imaging modalities as well as transcriptional and proteomic analyses have great potential to teach us more about recognizing and some day treating pre-clinical disease (Table 23).

Another area that is ripe for discovery is the relationship between genetic cause and phenotype expression. Consider hypertrophic cardiomyopathy, an autosomal dominant disorder. There are 10 different genes that carry literally hundreds of independent mutations that produce signs and symptoms that appear to clinicians as a single pathologic entity. Yet some of these patients will have profound deterioration in cardiac function and require cardiac transplantation, some will experience sudden cardiac death, and some will develop few symptoms with mild disease manifestations and live long and functional lives. Can we harness our knowledge of the considerable molecular diversity of causes of cardiomyopathy to define those patients who need an implanted cardioverter-defibrillator and those who will need only medical treatment? Can we determine if clinical response to pharmacologic therapies relates to underlying genetic etiology? In short, can we use this wealth of genetic discovery to inform our clinical decisions for patient management? To answer these critical questions requires collaborative study by cardiovascular clinician-scientists and basic researchers.

The discovery of genetic basis for inherited cardiovascular disorders has also allowed directed questions about clinically related heart disease of unknown cause. For instance, hypertrophic cardiomyopathy of the elderly is a well-described disorder with a related but usually distinct cardiac morphology from familial hypertrophic heart disease. Knowing the latter is caused by sarcomere gene mutations allowed studies to determine if elderly-onset

disease was genetically related. It would be hard to answer this question using family studies since parents of individuals with diseases that manifest late in life are often deceased. But we can begin to ask this question another way, by direct assessment of whether cohorts of individuals with elderly-onset hypertrophy have gene mutations. These analyses were remarkable: 20% of individuals with elderly-onset hypertrophic cardiomyopathy have a sarcomere protein gene mutation in the same genes that cause familial autosomal dominant and early-onset hypertrophic cardiomyopathy. Notably, the precise residues altered by late- and early-onset disease are not the same, implying that there are important biologic and perhaps biophysical differences in the consequences of different mutations in a given gene.

Genetics of complex traits. How do we use genetics and genomics to move from single-gene defects that cause cardiovascular disease to more complex traits, an area of intense investigation and excitement? One of the most productive approaches used to examine the genetic contribution to cardiovascular diseases that occur commonly in general populations are molecular association studies. Genomic libraries of SNPs provide information about sequence variants that are closely linked to virtually any gene. Study of whether particular SNPs are enriched in affected populations, therefore, can provide indirect analyses of the relevance of that candidate gene in cardiovascular pathology. While the success of candidate association studies in uncovering previously unknown molecules in heart disease has been limited, whole-genome association analyses hold more promise for success. These techniques take an unbiased survey of the genome for chromosome regions that contain molecules potentially involved in cardiovascular disease. One significant problem with these whole-genome association studies is that the number of SNP analyses performed to cover the entire genome is large. For sufficient statistical power to compensate for multiple testing, sample sizes must be huge. Further, to be certain that any association is valid, replication in an independent study cohort is needed. In part, these complexities will be solved with better architectural information of the human genome. For example, construction of haplotype maps (genomic regions that contain SNPs that vary in a predictable pattern in populations) will allow fewer genetic hypotheses to be tested yet still allow comprehensive interrogation of the human genome. Emergence of the human haplotype map (or hapmap) as well as the improved biostatistical algorithms and other statistical tools indicate that population genetics will continue to grow and to be powerful for defining new genes that are critical in cardiovascular pathology.

In the not too distant future, analyses will move from association studies that examine sequence variation or SNPs that occur throughout the whole human genome, to direct determination of the entire sequence of the human genome in patients. The speed at which whole-genome sequencing is becoming feasible is staggering given that in the 1970s DNA sequencing methodologies could define only hundreds of nucleic acid base pairs in a day. Technical advances in nucleic acid biochemistry and automation today allow the determination of 400 to 600 base pair routines in just hours. Whereas contemporary sequence approaches are based on selective analyses of particular DNA fragments, application of nanotechnologies and bioinformatics allows comprehensive genome sequence strategies. For example, total genomic DNA can be sheered and attached to millions of nanobeads on a microscope slide for individual amplification by polymerase chain reactions. Each individual nanobead serves as a platform for simultaneous fluorescence-based DNA sequencing of each DNA fragment. The millions of base pairs determined by DNA sequencing are then reassembled using bioinformatics. With further development these emerging platforms will soon allow researchers to examine a subset of genes or the entire genome in one patient or a large cohort of patients with heart disease. With the ability to have such a vast array of fundamental genetic data, cardiovascular clinician-scientists will have the opportunity to design powerful questions to test whether genotype informs clinical phenotypes and the risk for cardiovascular disease.

More sequence data on more patients with cardiovascular disease is unlikely to provide a simple solution to how and why heart pathologies occur. But this data will indicate strategies to discover signals that trigger genetic predisposition or risk into clinical disease. Development of animal models of human disease is likely to remain a critical approach to investigate pathophysiologic mechanisms. These models should serve as a test for novel therapeutics and will allow us to begin examining the modification of influences of disease expression, including genetic, environmental, or lifestyle factors.

Building better animal models. Contemporary approaches for modeling human cardiovascular disease largely rely on genetic engineering of mice. These models allow for the study of the mammalian heart with physiology that in large measure approximates human heart structure and function. With the discovery of a genetic risk factor for cardiovascular disease or possibly a human gene mutation, one can engineer the corresponding genotype into the mouse genome and assess longitudinal changes in cardiac morphology, cell biology, and transcriptional profiling. While this approach benefits from the extensive power of mouse genetics, this remains a very expensive and laborious endeavor. With considerable advances in comparative genomics, other organisms have emerged as excellent tools for studying human disease. The translucent zebrafish has been used by multiple investigators to examine genes implicated in structural diseases of the heart and vasculature as well as in pathologies such as hypertrophic and dilated cardiomyopathy. Zebrafish can be genetically manipulated through injection of morpholinos or oligonucleotides that are designed to disrupt normal ribonucleic acid (RNA) processing. The consequences of these manipulations can

occur within 72 h, allowing a rapid assessment of molecules potentially implicated in a particular cardiovascular disease.

With such wonderful models, researchers can delineate the cellular and molecular processes that occur early in the initiation of disease as well as later when compensatory mechanisms are also evident. A general approach to examining these processes is transcriptional and protein (proteomic) profiling. Cardiac expression of RNAs is analyzed by hybridization to gene sequences affixed to microarray slides (or chips). While this approach provides data about whether RNAs show increased or decreased expressed in the context of disease, microarray analyses are most robust when changes are large.

An alternative approach is to directly examine the number of RNAs that are present in the cell. This approach, termed Serial Analyses of Gene Expression (SAGE), capitalizes on the advances in high throughput determination of nucleic acid sequences. For example, to investigate the earliest changes produced by a human gene mutation that causes hypertrophic cardiomyopathy, my laboratory has over 70,000 different RNAs by SAGE that are found early and late in the disease. This SAGE dataset is a robust collection of molecules that has the potential to indicate the earliest signals triggered by a gene mutation that initiates changes, which ultimately herald overt disease. While today SAGE analyses are primarily used to study models of cardiovascular disease, this same approach could also be harnessed to provide a transcriptional profile of human heart tissues.

Proteomics. Transcriptional profiling will undoubtedly be strengthened by incorporation of proteomic information. Signaling pathways can be triggered or repressed by changes in protein activity as well as by changes in protein levels. To be able to identify the full impact on cell and molecular pathways that lead to cardiovascular disease, one needs to consider the activity of critical kinases and phosphatases, molecules that affect the function of target proteins and pathways by reversible phosphorylation. Proteomics allows the survey of protein levels and provides data on the modification state of these proteins. Proteomic analyses can be performed on selected subcellular fractions of cells, whole cells or tissues, or body fluids (blood, serum, and urine). Proteomic surveys are already being harnessed to examine heart disease. For example, proteomic analyses of blood taken directly from the coronary sinus of patients undergoing cardiac catheterization may provide novel insights into cardiac metabolism in health and disease. Proteomic analyses of serum in hypertrophic cardiomyopathy patients undergoing alcohol septal ablation for outflow tract obstruction may provide new information about the immediate response to acute myocardial infarction.

Conclusions. From genetics and genomics, from transcription profiling and proteomics, and from bioinformatics to bioengineering, there are incredible opportunities for cardiovascular discoveries. While no one researcher is able to master all of these techniques, compilation of these strategies through collaborative teams should provide powerful new advances for heart disease research. Cardiovascular investigators are well positioned to contribute in all arenas of this research program—as the physician who evaluates and performs patient interventions, as the discoverer of genetic risk and genetic disease, as the molecular modeler who elucidates disease mechanism, as the clinician who translates molecular discovery into patient care. With the power of modern technology and the talent of cardiovascular trainees, the future for improving our patients' lives has never been brighter.

Question and Answer

Dr. Fuster: I would like to get a sense of how you see the field evolving. We see the new technology that you are elaborating on; will you be able to tell us much more rapidly what is really going on in terms of associations and proteomics.

Dr. Seidman: Association studies that examine a single gene and assess whether or not it is fundamentally involved in disease pathogenesis have limited power and will likely give way to genome-wide association studies. I believe that the tools of modern genomics will make genome-wide association studies feasible and important. A critical issue, in which cardiovascular physician-scientists should become actively engaged, is how to define the cohorts for study. In other words, what heart disease phenotypes should we interrogate by genome-wide association? The more specifically we define a cohort of patients for study, the more likely they will share a genetic contribution to their disease. With the considerable advances in imaging and serologic markers of complex conditions such as coronary artery disease, we should be able to group patients into similar or dissimilar phenotypes better. This is important work that only outstanding clinicians can do, yet it is essential for productive genomic science.

Another interesting question is going to be whether variants in genes that cause monogenic disorders also contribute to the risk of common disease. For example, could some variants that in genes cause long QT syndrome also contribute to arrhythmias that arise only under stress? These scenarios of gene-environment interactions that contribute to disease are unlikely to be recognized as inherited traits. With the ability to rapidly sequence known genes that cause cardiovascular disease, researchers will be able to tease out more subtle associations.

We have also not addressed the ethical aspects of some genetic information. If you want to know how to look at an individual at risk for developing hypertrophic cardiomyopathy in the context of a family, right now, you can do echocardiography and an electrocardiogram serially until they are 40 years of age or you can do a gene test. The same approach is taken with long QT syndrome—serial evaluation or gene-based diagnosis. As clinicians we want to be certain of a diagnosis, but given gene-based diagnosis we may need to modify our management strategies. For exam-

ple, if a long QT disease gene is found in an individual who has had sudden death in family members, will you elect to implant a cardioverter-defibrillator regardless of symptoms? I think there are enormous opportunities to address these challenging questions in clinical medicine.

Question: For cardiac fellows who enter your lab, how much recent experience do you expect them to have prior to entering your lab?

Dr. Seidman: We have had fellows as well as very accomplished PhD scientists come to the laboratory who were initially unsure which side of a pipette goes into a test tube. Both have been successful. As an MD, I am aware of my clinical strengths and my experimental weakness. Many in the audience may know that I co-run the laboratory with my husband, a brilliant PhD scientist. We believe that we provide a complementary matching of talents to the laboratory, which has been productive. He examines research questions from a technical perspective, I examine them from a biologic and pathologic perspective. Although much of the proteomics, genomics, and bioinformatics language used in the research laboratory is at first intimidating to physicians, there is no need for this. It is like any new vocabulary. Once you have spent three weeks in the cardiac catheterization lab, you acquire the language and protocol appropriate for studying patients; the same is true in the basic science laboratory. There is no need to think that you have to have a PhD to do basic science.

Dr. Fuster: Say I am a first-year fellow at the University of Kentucky and I just listened to you. And I realize this is my field; I really want to work with you, and I give you a call. What advice would you give me?

Dr. Seidman: If someone wants to do what I call discovery research, where you are going to find out something that no one else knew before—to find a gene, for example—you are going to have to invest three to four years to do it. On the other hand, if you want to use the discovery information that someone else has already generated, you can begin to ask clinical questions as soon as you are ready to sign on to the lab. It is a matter of what you consider basic research. I do not think basic research is that different from good clinical research anymore; genetics and genomics are enormously interactive procedures. Go find the lab that is already doing this work and, if you do not have three to four years to discover a calcium-signaling program, ask another question that capitalizes on the information someone else has already generated.

Question: You mentioned earlier that you found genetics and genomics after some dismay you felt when treating heart failure patients. I am curious how clinical medicine plays a role in your career now. In other words, in advising future fellows who have varying interests, how does it all pan out?

Dr. Seidman: I continue to see patients. I no longer attend on the wards but I care for outpatients and for my hospitalized patients. I have tailored my patient population to be those individuals who have unexplained cardiovascular disorders. I see many patients with primary cardiomyopathies, known genetic disorders such as Marfan syndrome, and very few people with coronary disease unless they have atypical manifestation—very early onset, a very malignant phenotype that appears disproportionate to their risk factors. There is a great need for taking care of patients in the context of genetic disorders, and it is a great career track for researchers who want to continue to excel at clinical medicine by focusing on a particular niche.

Question: Senior investigators typically advise us to focus our attention on one theme. But as an early investigator, as a fellow, it is hard enough to find a project yet alone be focused in one specific area. Can you comment as to when you should know this is your area to work on and that it is time to focus?

Dr. Seidman: The rule is focus, focus, and focus, in the lab or in clinical medicine. The more you invest in a particular arena, the better you get at it, and the more you see breadth of disease and the opportunity to address the burning questions about the disease. So, focus is the way for you to become an expert and be the go-to person recognized by your peers within your institution and eventually outside your facility.

When beginning a career, however, it is wrong to focus until you are committed to a program. I tried several very different research projects before I decided that genetics was going to drive my career. PhD scientists have that opportunity to shop in their graduate programs. They go to different laboratories and pick up a couple different techniques and get a sense for each experimental system. Those of us with medical degrees do not do that so much, in part I suspect because of the long clinical training we have been through prior to starting some research. Yet, it is enormously important to be able to say when a research direction

Table 24. Women and Academic Medicine

Women in medical school	
Applicants to medical schools	46.6%
New entrants to medical school	45.8%
Graduates	43.2%
Women in residency programs	38%
Women in medical constituencies	
Internal medicine residents	39%
Cardiology trainees	10%
ACC membership	6%
AHA Clinical Cardiology Council membership	9.8%
Women faculty	
Tenured faculty who are women	15%
Percent of women who are tenured	16% (33% of men)
Of the 27,051 women faculty in 2002	
Professors	11% (31% of men)
Associate professors	19% (24% of men)
Assistant professors	50% (36% of men)
Instructors	18% (8% of men)
New faculty hires	36%
Faculty departures	30%
Department chairs	8%
Associate chair/vice-chair	19%

Source: AAMC data, 2000 to 2001.

or problem is not what you want to do and then shift to something else. It does not mean you do not want to do research, but it is wrong to stay and focus on something if you are not interested.

Question: How do you choose a good collaborator? A lot of scientists do not like working with clinicians because they believe clinicians have some kind of inferior understanding of science. The second part to this question is: how do you define the relationship of a collaborator? Who takes the lead? Is it you or the PhD scientist who has the original science you are asking for?

Dr. Seidman: Isn't this very much sort-of the same conflict that we see sometimes between the fellow and the senior resident and between the nurse and the physician at the bedside? How do you work with people? How do you figure out who is in charge, who is going to do the grunt work, and who is going to get the credit?

I do not think you necessarily choose a collaborator. You should plan to collaborate in all aspects of research. That means there will be lots of give and take. While you cannot demand that any researcher provide you the technology to ask a particular question, you can almost always structure an experiment so that it is a win-win situation for both individuals. That is how collaborations work best. I am less interested in who is going to be the senior author than getting the answer to the question we are trying to ask; let authorship issues work themselves out and be generous. Because you should look for collaborations with individuals who do not have your skill set, there will be a need for openness and trust. That way both collaborators learn from each other and advance the research agenda.

Question: You were mentioning, before, the concept of collaborative work and a team effort. You also made reference to the need for a niche physician who takes care of patients with these various genetic disorders. I was wondering what role those physicians play in collaborating with you and how they fit into the academic infrastructure, in the context of the challenges we have talked about at this meeting, in terms of promotion, and so on.

Dr. Seidman: Because of the way in which human genetics research has evolved, my laboratory first focused on relatively rare diseases. We found individuals with these diseases because we read papers authored by talented, academician clinical investigators. (Although clinical reports have somewhat fallen out of fashion, insightful detailed information about any disease remains a very important way to advance medicine and science. These point out the nuances of clinical disease that can initiate research questions that foster discoveries.) We have collaborated with clinicians from around the world. My responsibility to those individuals is that they are an equal partner and have the full authorship rights as somebody who is making the gene discovery. The publications from my laboratory often tend to have many authors listed; I think that is perfectly appropriate and indicates collaborative science.

You are also asking whether long-term collaborations affect promotions and academic advancement. This is an important question, one that cannot be globally answered, except to say that when each member of a team has demonstrated expertise in a particular area, promotion is less problematic. So become an expert and the go-to person in any collaboration and I believe your accomplishments will be recognized.

A related question is how to define a career track that promotes an individual who does not want to be in the wet lab but who can translate genetic discovery into clinical medicine. For example, what are the earliest signs of genotype/phenotype conversion? That is a good translational biology question that my laboratory cannot anwer. It is a fine project for a clinician who is well versed in genetics but not working in a DNA laboratory. Given the experience in clinical trials, the cardiac academic community knows the value of teamwork and that should help to solve collaborative issues when promotions come around.

Dr. Fuster: It seems there is a paper every week on polymorphisms and some specific disease or condition; then three weeks later something is published that refutes this completely. Is there a lot being published in genetics by a very small number of people, and is there confusion in the field?

Dr. Seidman: For association studies to be worthy of publication in a reputable journal I believe they need to provide statistical analyses to account for potential confounding issues such as multiple testing, and also demonstrate independent validation of the result in a second cohort. Until both are completed, the experiment is not done. The standards for publication of association studies is quite variable, and so yes, there is much confusion about genetic contribution to common cardiovascular diseases. I believe that with the newer tools that we discussed, more definitive information will be obtained that will hopefully reduce confusion caused by poor science.

Table 25. Gender Differences in Academic Careers: Faculty With Children

	Women	Men	p Value
Institutional support			
Research funding	46%	57%	< 0.001
Secretarial support	0.68 FTE	0.83 FTE	0.003
Publications	18.3	29.3	< 0.001
Self-perceived career progress	2.6	3.1	< 0.001
Career satisfaction	5.9	6.6	< 0.001

FTE = full-time employee.

XVIII. WOMEN AND ACADEMIC MEDICINE

Elizabeth G. Nabel, MD (National Heart, Lung, and Blood Institute, Bethesda, Maryland)

According to the Association of American Medical Colleges (AAMC), about one-half of medical school graduates are women, but there is a fall-off as you look at tenured medical school faculty (Table 24). Based on the percentages

Table 26. Institutional Support and Professional Outcomes

Variable	Adjusted Means*		Adjusted Mean Difference (95% CI)†	p Values for Effects	
	Women	Men		Gender	Interaction‡
Faculty with children, n	652	842			
Receive research money from institution, %	46.5	57.1	−10.6 (−16.4 to −4.8)	< 0.001	0.07
Secretarial full-time equivalents	0.68	0.83	−0.15 (−0.25 to −0.05)	0.003	0.08
Research assistant full-time equivalents	0.93	0.92	0.01 (−0.31 to 0.32)	> 0.2	> 0.2
Funded grants (1992 to 1994)					
Any grants, %	41.2	43.2	−2.0 (−6.7 to 2.8)	> 0.2	> 0.2
Grants, n	2.6	2.9	−0.4 (−0.8 to 0)	0.06	> 0.2
Total career publications, n	18.3	29.3	11.0 (−15 to −7)	< 0.001	0.04
Self-perceived career progress§	2.6	3.1	−0.5 (−0.6 to −0.4)	< 0.001	0.005
Career satisfaction‖	5.9	6.6	−0.7 (−0.8 to −0.5)	< 0.001	0.009
Faculty without children, n	297	160			
Receive research money from institution, %	51.4	51.0	0.4 (−11.4 to 12.2)	> 0.2	
Secretarial full-time equivalents	0.87	0.82	0.05 (−0.13 to 0.23)	> 0.2	
Research assistant full-time equivalents	0.90	0.74	0.16 (−0.15 to 0.48)	> 0.2	
Funded grants (1992 to 1994)					
Any grants, %	39.9	38.0	1.9 (−6.5 to 10.3)	> 0.2	
Grants, n	2.7	3.1	−0.4 (−1.4 to 0.6)	> 0.2	
Total career publications, n	17.6	20.5	−2.9 (−7.9 to 2.1)	> 0.2	
Self-perceived career progress§	2.7	2.9	−0.2 (−0.4 to −0.1)	0.01	
Career satisfaction‖	5.9	6.1	−0.3 (−0.6 to 0.1)	0.11	

With permission from Carr PL, et al. Ann Intern Med 1998;129:532–58. *Adjusted for medical school, specialty, race (majority or minority), year of first faculty appointment, age, and marital status. †The value for women minus the value for men of the same parental status. ‡Interaction of sex and parental status in a multivariate model for all faculty. §On a live-point scale on which 5 indicates faster progress. ‖On a 10-point scale on which 10 indicates higher satisfaction.

of women at different points of their medical training, women make up about 40% of internal medicine (IM) residents, but only 10% of cardiology trainees.

Once through medical school and training, how many women are choosing research careers? In 2002, Leon Rosenberg (32) of Princeton University co-authored a paper examining the gender gap in physician-scientists. His concern was to stimulate the number of physician-scientists in academic medicine in this country. To this end, he analyzed data obtained from the AAMC, the National Institutes of Health (NIH), and the Howard Hughes Medical Institute pertaining to the expressed research intentions or research participation of both male and female medical students in the U.S. The report documented a statistically significant decline in the number of men and women who have overtly expressed an interest in academic research careers in the decade between 1987 and 1997. Not only was there a decline in both genders, but women were less likely than men to be interested in a research career. Furthermore, while female medical student participation in the Medical Scientist Training Program and the Howard Hughes Medical Institute/NIH-sponsored Cloisters Program has increased, it lags far behind the growth in the female population in medical schools.

The researchers noted three worrisome trends in the research career intentions and participation of the nation's medical students: a decade-long decline for both men and women, a large and persistent gender gap, and a negative effect of the medical school experience for women. They concluded that these trends presage a further decline in the physician-scientist pipeline. As a country, we cannot afford to lose, in total, the number of individuals, men or women, who are interested in research careers, and it is critically important to pay attention to the issues of why people do not go into research, particularly women.

Not surprisingly, similar trends are apparent at the faculty level. The AAMC did a study that included data from 1976 and 1996. Among faculty who were first appointed in 1976, 22% of the men but only 10% of the women were eventually promoted to full professor. Women took longer to advance to full professor, sometimes twice as long. Based on AAMC data analyzing the 21,434 women faculty in 1996, 10% of women were full professors compared to 32% of men. Women were more likely to be associate professors, but if you look at the data for assistant professors and instructors, at this lower faculty level, women actually outnumber men (Table 25).

The AAMC also found that the disparities between men and women seem to grow even worse as you went on to senior leadership positions within an academic medical center, a hospital, or a university.

Barriers for women. On the surface, this may seem like depressing information, but I would like to be very practical and provide some reasons why this is the situation and propose some strategies that we, in academic medicine, can do to confront it.

Nancy Andrews, a faculty member at Children's Hospital in Boston, did a survey among her women MD/PhD students (33). She asked, "Are you interested in going into research? If not, why?" These are students who should be interested in research careers, because they are getting their PhD in addition to their MD. But the issues they typically raised included financial concerns, family issues, possible

unfair treatment, lack of role models, and a perception that research was not an attractive career pathway.

Furthermore, women in her survey perceived that it is impossible to combine a successful career with childbearing and a family life, an issue that should be important to both women and men, because the expectations of men entering academic medicine are more similar today than dissimilar to those of women. Most professionals will likely have a two-career family, and combining career time with family time is equally important for men as it is for women. Perhaps more women coming into the profession would help change the culture of the profession so that it will be more family-friendly, not just for women but for men as well.

Some of these barriers, however, are starting to break down. When Bruce Fye was American College of Cardiology president, he addressed the issue of women in cardiology on his President's Page in the *Journal of the American College of Cardiology* (34). One of the salient features as to why there were so few women in cardiology was what he described as a lack of critical mass: there were not enough women in the profession to really provide role models and mentors. He also felt that sometimes cardiology projected too much of a macho image, riding into town like John Wayne to "fix them and ride out." He noted that cardiology had an image problem in terms of balancing career and family life. He advocated that the subspecialty really must change to address both women's and men's concerns.

Career and family. Phyllis Carr and colleagues (35) have pointed out disparities in the way female and male faculty members are handled at universities. Prior to their survey, published in 1998, there was evidence that women faculty publish less, have slower career progress, and generally have a more difficult time in academic careers than their male counterparts; however, the relation of family responsibilities to gender in academic productivity was unclear, so she sent out a standardized 177-item questionnaire to full-time academic medical school faculty at 24 randomly selected medical schools. Based on 1,979 respondents, more than 90% of time devoted to family responsibilities was spent on child care, which was the same for both men and women.

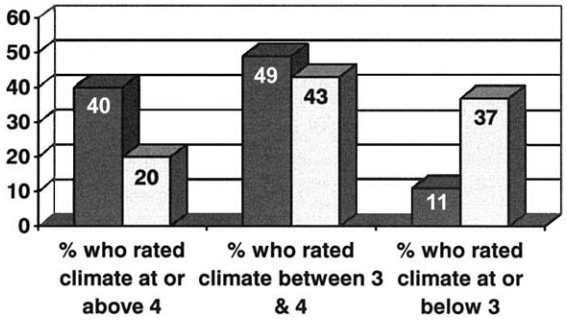

Figure 8. Distribution of department climate ratings by gender, on a scale of 1 to 5. With permission from the Report on the University of Michigan-Dearborn 2002 Survey of Academic Climate and Activities (37). **Dark bars** = males, n = 68; **light bars** = females, n = 42.

Among faculty with children, women had greater obstacles to academic careers and less institutional support, including research funding from their institutions (46% compared with 57%; $p < 0.001$) and secretarial support (0.68 full-time equivalents compared with 0.83 full-time equivalents; $p = 0.003$), than men (Table 26).

Similarly, compared to men with children, women with children had fewer publications, slower self-perceived career progress, and lower career satisfaction. The survey also confirmed previous observations of no significant differences between the sexes for faculty without children, suggesting that perhaps the playing fields are more level when children are not a factor. The authors concluded that, compared with female faculty without children and compared with men, female faculty with children face major obstacles in academic careers. Some of these obstacles can be easily modified (for example, by eliminating after-hours meetings and creating part-time career tracks). Medical schools should address these obstacles and provide support for faculty with children.

Not surprisingly, the family issue is not only one of devoting time to childcare but also related to geographic mobility (36). Two-career families probably have experienced this already, in terms of choices about where to go for training. This issue is heightened when there are choices about where to establish a research career or a clinical practice. In a study by social scientists at the University of Michigan, women scientists were much more likely than men scientists to be in a two-career marriage, and scientists in two-career families were less likely to migrate than a one-career family. Also, the evidence suggested that while family constraints on women scientists' careers generally appear to be weak, it becomes acute when they have children. Specifically, women with children were less likely to have the geographic mobility to pick up and move from one place to another; however, it is important to keep in mind the big picture. Obviously careers are very important, but never underestimate the importance of family and the satisfaction that it will give you if you choose to have a family as you go through your career.

Before considering strategies, let us address some of the concerns Nancy Andrews raised (33). Regarding financial concerns, the NIH Loan Repayment Program is a fantastic program, and I encourage anyone concerned about repaying debt when you're working towards a research career to apply for the Loan Repayment Program. The acceptance rate is very high, and information can be found at the NIH web site (www.nih.gov). Another financial concern is that academic salaries must be competitive with practice salaries. Given recent changes in many practice salaries, academic salaries are becoming increasingly competitive.

Addressing family issues. What can be done to address family issues facing both men and women? First, we can lengthen the tenure clock if women or men need more time because of family issues or whatever; the tenure clock should not be a problem. Also, leadership should be sensitive to

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early morning and late afternoon meetings that affect the ability to drop off or pick up a child from day care. The involvement of your significant other is very important, as those with two-career families will learn very quickly that things have to be done in a compromising fashion for everything to work. Addressing ongoing family issues is something neither spouse can do individually.

Will I be treated fairly? That's a question that is asked regularly by women. It is important to have some degree of transparency of salaries, resource allocation, and promotion; anyone should know the criteria for appointment as a lecturer, an instructor, or an assistant professor. What is the standard package that comes with that recruitment? What are the expectations in terms of academic promotions? If you do not know the answer to these questions, ask. As you begin your academic appointment, understand very early on the criteria for promotion and develop a professional curriculum vitae that contains objective documentation of your academic accomplishments.

I cannot emphasize enough that there has to be an absolute commitment to the promotion of women and minorities throughout the academic ranks of senior leadership within an institution. In a study conducted among scientists and engineers at the University of Michigan, some of the conclusions were that female assistant professors in science and engineering received less mentoring than other groups; women had a higher service rate on formal committees than men, but did not chair the committees at a higher rate; and women received fewer items in their renegotiated contracts than their male counterparts (37). The perception created by the data was that women were not being treated equally, and this was apparent in gender differences ranking the "department climate." Compared to their male counterparts, women rated their departments significantly lower on gender egalitarian atmosphere (e.g., the environment promotes adequate collegial opportunities for women, and women are appropriately represented in senior positions) (Fig. 8). A number of similar studies have emerged at other universities. It takes senior leadership to seriously address the issue.

For investigators just starting their research careers, what is the future likely to bring? Perhaps the numbers are not where they should be in terms of the number of women in academic medicine, but the numbers are improving all the time. There is now a critical mass of women in IM, just as there has always been a critical mass of women in pediatrics and psychiatry. The number of women in cardiology is rising. It is not where we need to be yet, but it is getting better.

Career strategies. Why do I think the climate for women is improving? To put it simply, we cannot afford to lose the next generation of physician scientists, men or women, and based on widely reported findings in the last few years regarding hormone replacement therapy and women with heart disease, women are now demanding to see women cardiologists.

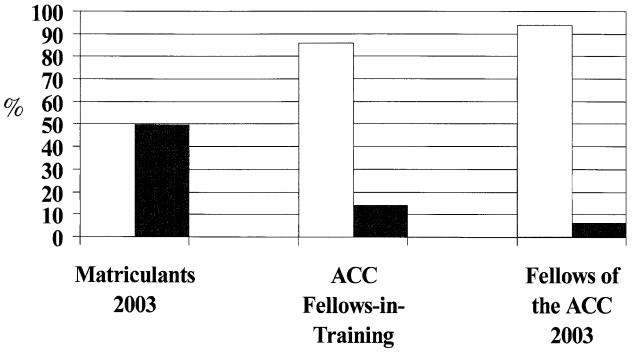

Figure 9. Matriculants, ACC fellows-in-training, and ACC fellows. Source: ACC and Association of American Medical Colleges Data Warehouse, 2003. **Open bars** = men; **solid bars** = women.

As you formulate the strategy for your scientific career, there are several personal-level issues to address. For me, the most important issue is finding your passion. Just find what you love doing, then go out and give it your best. At the same time, it is very important as we go through our careers to assess our strengths and our weaknesses. You have to be willing to take a realistic look at yourself and say, "This is what I like to do, while this other area is more difficult for me." I always encourage people to lay out a game plan, not big details, but more of a sense about what you want and where you want to go, including both short-term and long-term goals. Then focus, focus, focus. There is a productivity equation: productivity is equal to the amount of work you put into something divided by the amount of distractions you have. Trying to be all things to all people by doing a lot of different things will prevent you from being truly focused on the couple of things you want to do in your career. But be an active participant. That does not mean you have to serve on every committee or be all things to all people again. But consider what things you can do within your division to demonstrate good citizenship, given your interests and time constraints.

Conclusions. As women, we have an extraordinary opportunity to be gainfully engaged in our profession. It may seem, at some times, that it will take us awhile to get there, but I assure you that the rewards and satisfactions are tremendous. I enjoy reading biographies about women and their lives and the issues they faced and had to address. I recommend the story of Jill Ker Conway in *The Road from Coorain* (38). Jill Conway went from the despair of a very brutal, physical life during the Depression on a sheep ranch in Australia to eventually becoming the first woman president of Smith College. There is another wonderful story about Anne Martindell, who was told, at age 20, by her father, "Anne, you have got to drop out of school. You are too smart. You'll never get married. No man will ever want to marry you" (39). She did. She went on and raised a family and, in later years, went back to school, earning her undergraduate degree from Smith College at age 87. That's a testament to the importance of education and persistence.

Academic medicine is a richly awarding career. We all have a number of choices within medicine, but we shouldn't lose sight of how fortunate we are, as evidenced by the genuine goodwill that exists now among leadership in academic institutions who are looking to make the playing field equal for women in academic medicine and help us all succeed.

XIX. PANEL DISCUSSION: GREATER REPRESENTATION FOR MINORITIES AND WOMEN IN CARDIOLOGY

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Harlan M. Krumholz, MD, SM, FACC (Department of Medicine [Section of Cardiovascular Medicine, and the Robert Wood Johnson Clinical Scholars Program], and Epidemiology and Public Health, Yale University School of Medicine, and the Yale-New Haven Hospital Center for Outcomes Research and Evaluation, New Haven, Connecticut)
Elizabeth G. Nabel, MD (National Heart, Lung, and Blood Institute, Bethesda, Maryland)

Dr. Fuster: We all know of the good work done by the Robert Wood Johnson Foundation. Why are there not five foundations like that? Should we develop advocacy to see more of these foundations developed?

Certainly, there are very successful people in this country who should be approached to see whether we can engage them in something like this. It requires passion. We need to target certain individuals to ascertain their interest in developing a foundation like that where we can attract more minorities. It has been done; we just need to do more of it.

Dr. Bonow: The issues are really complex. This is where we need to be focusing some of our attention, including getting to young people very early, in high schools, identifying minority students, and getting them turned on to science. Perhaps foundations can help us do that, although there are governmental issues here, too. But we must find ways of getting high school students interested and help them get their education on the right trajectory towards a career in research. If we focus most of our attention on just trying to get medical students or residents interested in careers in research, it is too late at that point.

Dr. Nabel: The National Heart, Lung, and Blood Institute (NHLBI) has a program called BRTPUG, Biomedical Research Training Program for Underrepresented Groups. We bring kids in at the high school level, and then we essentially take care of them throughout the remainder of their career. It has been very successful.

Dr. Bonow: I knew NHLBI was doing something on a smaller scale, but maybe we could think of larger scales.

Question: I have two questions. Number one: Are there any opportunities specifically for people interested in women's studies, such as the study of cardiovascular disease in women? And number two: Are there research funding opportunities for women in cardiology?

Dr. Nabel: I am happy to say that the NHLBI is the administrative home for the Women's Health Initiative (WHI) (http://www.nhlbi.nih.gov/whi/), which is a very broad-based research program on women's health issues. We sponsored recent studies on hormone replacement therapy. I think it is the intent of the Institute to continue to support and sponsor the WHI. So, that provides a great opportunity to conduct research on a variety of issues related to women. At National Institutes of Health (NIH), there is also the Office of Research on Women's Health, directed by Dr. Vivian Pinn (http://www4.od.nih.gov/orwh/). They are involved very broadly in a number of research and educational programs.

Your question about whether there are funding programs specifically for women investigators is a good one. I do not know the answer to that, but I do not think so.

Dr. Bonow: I do not believe there are any funding mechanisms, but I would strongly encourage you to look at both the American College of Cardiology (ACC) (http://www.acc.org/) and the American Heart Association (AHA) (http://www.americanheart.org/presenter.jhtml?identifier=1200000) websites, because there are committees for women in cardiovascular disease and they can be helpful if you are looking for a career in research. Certainly this is a big issue. If 50% of medical students are women, we do not find that 50% of the cardiology fellowship applicants are women (Fig. 9). We have a major workforce crisis right now in terms of providing enough doctors to provide cardiovascular care, and it's going to get worse with the baby boomers growing up.

Both the AHA and ACC have major efforts underway to identify some of the issues Betsy was talking about and determine how we overcome those. At the AHA, it's more geared toward the investigators and researchers. There is a women's luncheon every Tuesday of the annual AHA meeting, and there is travel support available for eligible women fellows to go to the meeting for free and attend that luncheon.

Dr. Nabel: Many of the AHA councils now have a women's committee. The Clinical Cardiology does, as does the Council on Arteriosclerosis, Thrombosis and Vascular Biology (ATVB). The Clinical Cardiology Women's Committee is very active and offers travel awards. The ATVB also has a luncheon at the annual meeting and gives out a number of research and travel awards. Networking through an AHA council is a good way to access that information.

Dr. Fuster: Harlan, let us say I am a fellow who wants to pursue a career in epidemiology. It seems to me that what happens, at least in dealing with fellows, is that they reach the stage in getting a degree where they can understand epidemiology, statistics, and so forth. They work on some studies, but they are mostly anonymous because these trials may involve thousands of people. Are those of you who made it into the field of epidemiology unique? What kind of an approach would you advise?

Dr. Krumholz: It is challenging to develop a research career where you are trying to establish yourself, obtain funding, and address important questions. The rewards are substantial, but in the beginning, especially in large collaborative studies, it can be difficult to distinguish yourself and develop an early body of work that is known as your own. Some of the best research now is conducted in the context of these large teams, but they work best when there are ample opportunities for people, particularly young investigators, to play prominent roles in substudies that address worthy research questions. These opportunities rarely just land in your lap. It is important for young investigators to develop a research plan, and seek opportunities and mentorship. You can avail yourself of people locally or around the country; people who you think are doing interesting work. You will be surprised how receptive individuals will be in talking to you. You need to find senior people who can guide you with advice and opportunities, and help you see how you can best be successful. You need to bring energy, ideas, and a willingness to work hard.

Perhaps the most important issue is for you to decide what you, as a young investigator, are most passionate about investigating. If you become immersed in a large research project, there is a possibility that you can become somewhat anonymous. At Yale, while we are helping young investigators get experience doing research, we are asking them: if you were going to write a paragraph characterizing yourself, what would it say? What are you really about? What is it that you are trying to accomplish in your career? I have done this with fellows and with faculty, people who are still trying to formulate their interests and direction. For the young investigator, there are many questions. You have got to have a sense of what the field is. Who has come before you? What are people in the field currently doing? What are the themes of research underway, and what kinds of skills and opportunities exist for you? What do you want to do? Then within that general framework, you have to find a niche for yourself, and that niche may evolve over the course of your career. But if you can define who you are and what you are trying to accomplish, you can be very successful. But you have to be resourceful and tap into those people who can help direct you and give you advice.

These large projects can be great opportunities, but mentors need to help young investigators ensure that they are not just employees, but are having the chance to develop their career. Of course, goals will vary by individual and it is important to determine if you are interested in eventually being an independent investigator or whether the goal is to continue to be a contributor to research, but not in a leadership role. And this gets back to being able to describe who you are and what you want to achieve with your career.

Dr. Bonow: That is a great response to what people need to do with their careers no matter what they are going to do; however, if they want to get into outcomes and health policy research, you mentioned they need specialized training. Can you define that training? If they are already in a fellowship program, they may or may not be in a program that has a K30 or other means of providing this. What is necessary for these people to get the tools they need?

Dr. Krumholz: I have always thought of this not in terms of degrees but in terms of skills and competencies. To be successful in the long run, you need to have a very deep understanding of clinical research design and biostatistics. You have to be able to invest yourself in understanding the medical literature and to understand the strengths and weaknesses of what is published, and you have to be an outstanding clinician who knows the challenges of clinical care and the needs of patients. Sometimes interns come to me saying they want to do research. I tell them to spend the next two years becoming the best clinicians they can because that is going to be the fundamental next step to becoming the very best clinical investigators they can be.

My general advice: start the clinical cardiology fellowship; become an outstanding clinician; then start building the next steps in terms of those specific skills I laid out; and decide what you want to do. You may go more in one direction, and you will need deeper skills in that particular area. But the point is that there is a range of institutions around the country with the capability to train you and provide mentorship as you develop this. If you are not at one of those places, you need to move, or else your chances of success will be greatly compromised.

Dr. Nabel: Do you recommend people get a masters degree in public health (MPH)?

Dr. Krumholz: The degree is not as important as the knowledge and skills that are gained. An MPH or master's degree in another subject can be a good way to gain these fundamental skills, but I have also seen people who obtained degrees but seemed to have missed the opportunity to acquire skills and insight. The drive to learn is what is important, and a degree can often be helpful because of the structure and content of an established curriculum and an access to teachers, but it is not the only way. In my career, my opportunity to pursue coursework at a school of public health was critical to my development as an investigator. I did obtain a master's degree, but the goal per se was not the degree but the experience that led to the degree.

Dr. Fuster: It is interesting because all of you give much more importance to the goal you want to achieve than the instruments of the process. And that is reality: first you need the passion, the drive, and then you find a process that gets you where you want to go.

Dr. Krumholz: You have ultimately got to put yourself in a position where you will not be denied. There are so many challenges along the way; you must have that internal sense that this is really what you want to do with your life, and then find people who can help you do it.

Question: My question pertains to what you have been touching on right now, which is the methodological training. Clearly, and especially for those of us who are more advanced in our training, it has been eight or nine years since we have done epidemiology. Unfortunately, I do not think there is anything more than a rudimentary introduction to epidemiology in most fellowship programs. So, 1) does your institution provide anything different? And, 2) short of getting a public health degree, is there anything that a clinical fellow can do in terms of finding a program where they can be sponsored for three months and get some basic skills like those you described?

Dr. Krumholz: That is a really good point, but it is first important to realize that you never stop learning. It is not a matter of getting a certain set of skills that are going to stand you in good stead the rest of your life. I am doing research now using methods I did not know when I was a fellow. I continue to learn from the people around me. Another important point: unlike people who did research 30 years ago who could sequester themselves and tinker with whatever they were doing and still produce insights, the very best research today is being done within teams in which there is multidisciplinary collaboration. The best situation puts you in a position where you are working with people who are specialists in particular areas and yet can work together for common goals.

By the way, getting teams to work well is a very important research skill. How do you make sure people on your team feel appreciated, engaged, involved? How do you foster the necessary communication? How do you work together for common goals? Those are important organizational skills that will lead to great success within research.

Part of acquiring the skills you need is your attitude. Are you developing your own critical thinking skills? Are you in a classroom environment where people are willing to go beyond superficial knowledge to a place that demands you really dig deep and understand? What is the basic philosophy? You are not going to be completely knowledgeable about everything, but you must have a certain attitude towards obtaining the knowledge and skills that will be required to successfully pursue your projects. There are various places around the country that encourage this kind of attitude—these places push you, and engage you intellectually. It is the context and environment you put yourself in that will help you raise the level of your game. You should be trying to acquire those skills in a way that is not just, "I am looking for the degree," or "I am finishing this course," but you are really asking questions of yourself and others. It is putting yourself in a position to be a tough critical thinker and giving yourself an attitude about knowledge acquisition.

Dr. Fuster: So, in summary, you ask Harlan for a job and go to work with him.

Dr. Bonow: That is a good option, actually. But if you cannot get a job with Harlan or you are not in one of those programs, but you are really serious about it, there is a 10-day course every summer on epidemiology, sponsored by the AHA's Council on Epidemiology and Prevention. The faculty is there with you for the entire 10 days. It is a crash course, but it's very thorough in how to do clinical trials; what epidemiology is all about, and methods involved in data analysis—all taught by the experts in epidemiology.

Question: My question is about fellows such as myself who are not in an investigator track but are interested in doing translational research, such as gene therapy or stem cell biology in our second and third years of fellowship. At this point in our careers, is it more important to get experience in the basic science side or in the clinical research side, or is it possible to get experience in both at this stage of our fellowship?

Dr. Nabel: You need to think about what you want to do long term: Do you want to practice medicine or be engaged primarily in research? As Harlan said, I really view this as being a part of a research team. If you see yourself practicing medicine, then you are going to want to partner with a basic scientist to help bring those ideas forward and do phase I or II studies. That means you will want to get training in clinical trial design and clinical data analysis.

On the other hand, if you want to spend your time primarily doing research, eventually bringing things forward to the clinic, but you would rather hand it off to a clinician at that point, then you will want to spend time in a laboratory and learn molecular and cellular biology. That is going to give you the basic tools to learn how to handle cells, manipulate them, prepare them for clinical production, work with or develop animal models, do studies, and so on.

Dr. Fuster: It is the issue of whether you want a more clinically oriented approach or a more basic research-oriented career, and your future very much depends on the clinical skills you obtain along the way.

Question: It seems like a lot of us are already H05, H06, H07, H08s, and many of you were talking about basic science and outcomes research that might require two or three additional years. Can you address the issue of the length of fellowship and how to deal with that?

Dr. Krumholz: In part, it is a matter of customizing your education to your own needs. For example, people who make decisions and differentiate earlier can do things like short track through internal medicine. Many people working with me now are doing four-year fellowships—two years clinical, two years research—where they continue gaining some clinical exposure during part of that research time. Everyone has their own needs, and it really depends on your own niche, what opportunities you can find, and how you can put it together for yourself. People also have different financial pressures and so forth, but it is a matter of long-term perspective. Some people opt out early, because they do not want to spend that time on education and training, but then they are bored 10 years later

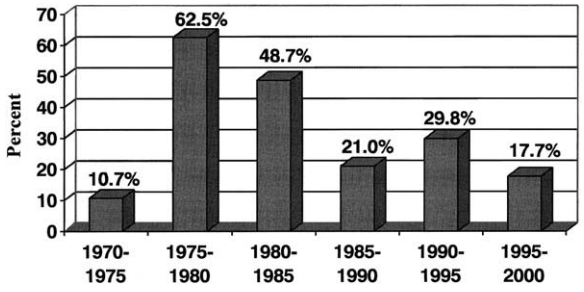

Figure 10. Percentage growth of international medical graduate practicing cardiologists. Reprinted, with permission, from Zoghbi et al. (41). Source: American Medical Association. Physician Characteristics and Distribution in the U.S. 2002–2003 Edition, Chicago, IL: American Medical Association 2002.

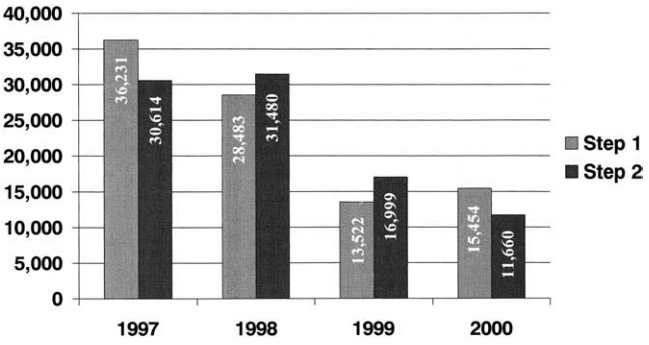

Figure 11. International medical graduate (IMG) registrations for the United States Medical Licensing Examination (USMLE) step 1 and step 2 examinations. Reprinted, with permission, from Zoghbi et al. (41). Available at: http://www.acponline.org/journals/news/sep01/imgs.htm, Maguire P. ACP-ASIM Online, 2001.

with what they are doing and they are not finding the same fulfillment they might have had if only they had invested the time and gone in another direction. Ultimately, opting out early ends up being a short-term gain, but it could sacrifice long-term satisfaction.

Think about what you are really aiming for. The big win here is to find something that thrills you for the rest of your life, where it does not feel like a job and you are never bored. You get that big win when you find yourself in a position where every day you feel that you are making a contribution; every day there is something exciting and stimulating going on. Then, whatever you are talking about in terms of an extra year or two at the front end falls away because of what you ultimately want to achieve. Some people are going to thrive in clinical medicine, and they should do it. Think about what fits your personality type and what gets you excited, because it would be unfortunate to make that decision early on and find yourself needing to retire early in order to find other things that will stimulate you. These careers that the people here have found: these are careers where there will be no retirement. That is what you want to find.

Dr. Bonow: It is a real issue. My question is this: if it is OK to short-track and get two years of medicine if you are in a research track, why does any cardiologist then need three years of internal medicine if that person knows right from the get-go he wants to be a cardiologist? Dr. Fuster, probably more than anybody else, has been trying to work on streamlining training programs so that it is only maybe two years of internal medicine.

Question: What is the relative weight of fame in the academic pursuit? How does that compromise the original search for truth, which is our original passion? And in talking about fame, how big is the limitation that is imposed on people who are not coming from famous universities in terms of getting a faculty position at a decent place. Are there limitations when you apply for a grant because you are applying from a less famous institution versus a famous institution?

Dr. Nabel: There are a lot of different levels to your questions. Let me start with the last part first. As an institute, we are extraordinarily sensitive to the fact that if we want science and medicine to go forward, we cannot concentrate resources in the hands of a few. Resources must be distributed equally across the population in this country. We work very hard to try to achieve that goal. Grant mechanisms are set up recognizing that grant applications may come from individuals or institutions that do not have the same level of resources that others have. We go out of our way to try to help provide those resources. So, at an NIH funding level, people are extraordinarily sensitive to those issues.

Am I going to get a job if I come from a university that may be less known than another? For many of us who have had the privilege of being able to hire people, you are never made by the name of an institution; you are made by who you are. You are made by your character, your passion, your drive, what you've accomplished in your life. People who hire understand that and are absolutely going to look at the individual, not a set of credentials. That is my perspective.

Dr. Fuster: His first question is a very important one: the question of compromising a genuine creative approach towards discovery that you have at a young age versus being more engaged in who you are and what the world thinks of you. That is a great question for young people.

Dr. Krumholz: Ultimately, it all depends on you. There are people who become enamored of certain peripheral elements, and there are other people who are able to stay true

Table 27. IMG Cardiology Residency Trends

	IMG (% of All Trainees)		
Year	General Cardiology Trainees (%)	Clinical Cardiac Electrophysiology (%)	Interventional Cardiology (%)
1996	36.6%	18.5%	NA
1997	40.0%	33.7%	NA
1998	42.0%	44.6%	NA
1999	41.2%	48.4%	39.7%
2000	38.6%	37.2%	55.8%
2001	36.7%	43.0%	49.1%
2002	32.9%	41.7%	42.1%

Reprinted, with permission, from Zoghbi et al. (41). Source: JAMA Annual Medical Education Issue. JAMA, 1997 to 2003.
IMG = international medical graduate.

to their beliefs and core values. I will say this: if you are going to be successful in academics, you have to get used to failure. It is an incredibly humbling profession, because you are seeking truth all the time and you are frustrated at many different turns. Whether it is a grant application or a paper you want to have published, whether it's seeing the impact of your work truly translated to the benefit of individual patients or it all gets lost or ignored, you have got to be able to withstand. In fact, in the end, it is not that you feel so empowered, but that you are constantly struggling to make a difference.

The people who are doing it best are constantly striving to generate the knowledge that is going to make a difference. The people you end up respecting the most around you: it is not so much about them; it is about ideas. It is about trying to let the ideas fight for themselves. One of the most wonderful things about this, in terms of what you are saying about universities, is that somebody could be working anywhere in the U.S. who could come up with some very insightful ideas that will see the light of day and maybe turn a whole field on its ear. With persistence and good ideas, you can make a difference wherever you are and wherever you are from.

Dr. Bonow: You all addressed the ego question quite well. If your ego's too big, then you are not going to be able to withstand failure. Ego is necessary, but also you have all been around long enough to see people with various-sized egos and how they respond. Go back to Harlan's initial comments about the people you want to be like and the way you want to lead your life. You need enough confidence and ego to go forward, but keep it all in perspective.

Dr. Fuster: Also, fame is not a job, fame alone cannot sustain you. You go through failures, and your colleagues, who helped you succeed or not, know exactly who you are and what you do. It is not a free system in the U.S: you are reviewed constantly and in a way that answers the very questions you presented.

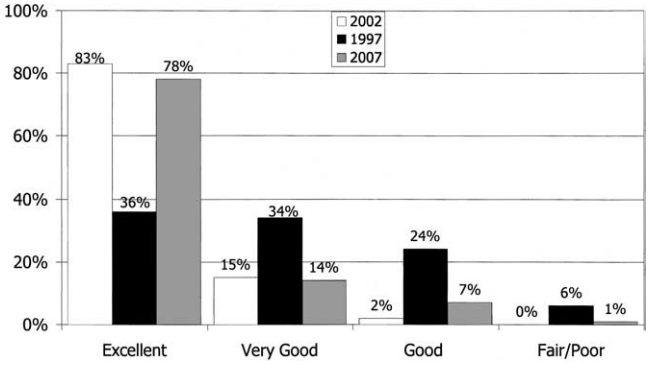

Figure 12. Job opportunities for senior fellows. Training directors, n = 137.

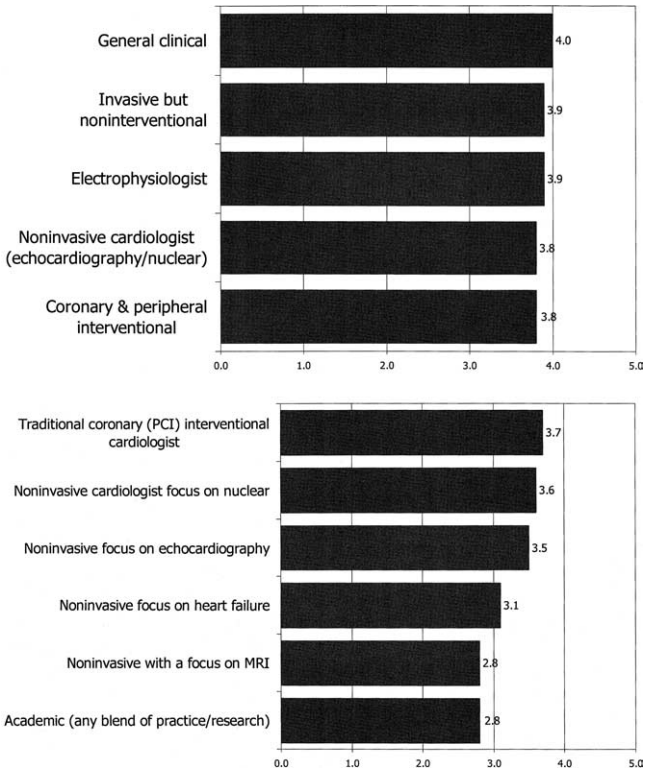

Figure 13. Mean ratings on the demand for various cardiovascular practices. 5 = very high, 1 = very low. Recruiting firms (n = 113). Source: ACC Cardiology Workforce Study 2002 and Cardiology (43).

XX. OPPORTUNITIES IN TRAINING AND CAREERS FOR INTERNATIONAL MEDICAL GRADUATES

William A. Zoghbi, MD, FACC (Echocardiography Research, Baylor College of Medicine and the Echocardiography Laboratory, The Methodist DeBakey Heart Center, Houston, Texas)

Since the 1960s, international medical graduates (IMGs) have constituted an important part of the health care workforce, currently filling about one-third of cardiology training positions and about one-fourth of clinical practices in the U.S. International medical graduates are physicians in postgraduate training or in practice (who completed their medical school training outside the U.S., Puerto Rico, or Canada). They are either foreign nationals on special visa status (e.g., J-1, H-1, or F-1) or U.S. citizens or permanent residents who graduated from foreign medical schools. The misconception is that all IMGs are foreign nationals; in fact, 53% are U.S. citizens or permanent residents in the U.S.

Some impressive statistics illustrate the importance of IMGs. Their influx during the last 40 years has been due largely to unmet needs in rural areas. Besides being an important source of manpower for underserved areas, IMGs also fill unmet needs in both teaching and research. Consequently, IMGs now comprise nearly 25% of all cardiologists in the U.S. and make up about one-third of all cardiology training positions. The ethnic and cultural diver-

Table 28. Visa Options and Other Requirements for International Medical Graduates

Research No Patient Care	GME Training	Academic Clinical Practice
Visa Options*	Visa Options*	Visa Options*
• J-1 "Research Scholar"	• J-1 "ECFMG"	• H-1B—Intl. Renown
• H-1B—employer	• H-1B—employer	• H-1B—limited
• NAFTA	• U.S. medical school graduates: F-1/H-1B	• H-1B—unrestricted
• B-1 if a scientist sent from abroad		• NAFTA—limited
		• O-1 unrestricted, hard to obtain
Other Requirements	**Other Requirements**	**Other Requirements**
No U.S. medical exams	USMLE 1 & 2	Academic license or USMLE 1 & 2
No state medical license	USMLE 1, 2, & 3	USMLE 1, 2, & 3
	ECFMG certificate	ECFMG certificate
	State limited or training license	Full state medical license

*Unless indicated—all visa options are for non-U.S. permanent residents. Prepared by Michele Stelljes, MA, Senior Immigration Advisor, Baylor College of Medicine; intended for general informational purposes only and should not be used as the sole source of information for decisions regarding legal status or rights.

sity they provide is very important. Interestingly, they proportionally contribute more women, especially women who are foreign nationals, to the physician workforce than do U.S. medical graduates.

From 1980 to 2000, the number of U.S. cardiologists who were IMGs increased by 175% to a total of 6,178 out of a total workforce of about 26,000 cardiologists (Fig. 10) (40). The number of IMGs is even higher in other disciplines, particularly internal medicine. Overall, the total number of active IMG physicians in the U.S. stands at about 196,000, which is a doubling of IMGs over the past 20 years. Two countries with high representation of IMGs are India (18% of active IMG physicians) and the Philippines (9%); IMGs from Spanish-speaking countries are underrepresented, with only 5% of IMGs from Mexico. This is an interesting fact, given that the Hispanic population is the fastest growing minority in the U.S.

One of the many challenges that IMGs face, either during training or in their careers, is whether they can stay in the U.S. and practice in this country.

I chaired the American College of Cardiology (ACC) Task Force on International Medical Graduates at the 35th Bethesda Conference (41). I want to share some of the information that emerged from this task force, because physicians in training, in practice, or in academic settings may not be familiar with some of the issues facing IMGs. Also, it may be helpful to understand the complex issues being addressed regularly by faculty and program chiefs in terms of immigration-related problems and efforts to retain IMGs, especially those in academic careers.

Current challenges. The first major challenge is certification, which requires passing steps 1 and 2 of the United States Medical Licensing Examination (USMLE) (http://www.usmle.org/), a new English proficiency test, and the clinical skills examination (CSE) of USMLE, which was implemented in 2004 to replace the clinical skills assessment test of the Educational Commission for Foreign Medical Graduates. As part of the USMLE Steps examination, the CSE is now offered in five U.S. cities: Atlanta, Chicago, Houston, Los Angeles, and Philadelphia.

There are restrictions, limitations, and perhaps financial implications for IMGs to consider, such as a more prolonged and difficult process for obtaining a visa to the U.S. By 2000, the number of foreign medical school graduates entering the educational pipeline had sharply declined, based on the number of IMG registrations for the certification examinations (Fig. 11) (42); however, the pool of applicants is still quite high, with IMGs making up between 37% and 42% of residents coming into cardiology in recent years, and the trends are similar for subspecialties (Table 27).

There is some duplication of medical training and costs for physicians who have had postgraduate medical education (e.g., internal medicine, cardiology) in international training programs. In terms of the performance of residents going into fellowships, the cohort of IMGs overall has done well, and probably slightly better than U.S. medical graduates. This is likely because there are a number of selection processes IMGs must pass through before coming to the U.S. as well as the repeat training these individuals are likely to experience.

Following clinical training, if an IMG aspires to have a career in the U.S., employment will depend upon whether an individual has a J-1 visa. The J-1 visas are harder to get because immigration laws have changed over the past few years, based on more stringent restrictions in place since the attacks of September 11, 2001. Consequently, the greatest risk many IMGs face as trainees is not being able to join the workforce, which pertains largely to the 27% of IMGs in the J-1 exchange visa program. This program requires visa holders to return to the country of origin that has sponsored their coming to the U.S. for two years; J-1 visa holders are at increasing risk of not finding waivers.

Task force recommendations. Recommendations from the ACC Workforce task force included maintaining the current IMG workforce distribution, particularly if quality and performance remain high. Another recommendation is

to provide more accessibility to the USMLE examinations, which might include expanding further the number of cities where testing is done, and perhaps offering some scholarships. Short-tracking of individuals may be attempted in a pilot project that would decrease the total amount of training required of IMGs, particularly if they had internal medicine and cardiology training abroad. A final recommendation is to involve the ACC, the American Medical Association, and other organizations into looking at influencing IMG immigration laws, particularly to find a balance between IMG training and the ability to remain in the U.S.

The task force also wants to facilitate international exchange programs of physicians; IMGs staying in the U.S. could give back to their countries. For example, IMGs in the U.S. might be required to return for short and extended periods to contribute to health care in their country of origin—for instance, in the form of sabbaticals, teaching opportunities, or performing unavailable procedures. Part of this might be an exchange process that would recruit U.S. graduate colleagues to serve in a similar capacity, thus serving to enrich the experience of U.S. physicians and their colleagues in other countries.

Career opportunities. During the summer of 2002, the ACC sent surveys to senior cardiology trainees, cardiology training program directors, recruiting firms, and a sample of domestic ACC members (43). According to responses from 137 U.S. training directors, there are outstanding job opportunities in academic medicine or clinical practice for senior fellows, and this is expected to continue for at least the next couple years (Fig. 12). As to the ease or difficulty in recruiting qualified cardiologists, 113 recruiting firms responded, and 76% were finding it "very difficult," and another 21% said it was "somewhat difficult" to fill cardiology positions. About one-quarter of senior fellows say they are interested in academic medicine, while about one-half say they are interested in single-specialty practice. Looking at the demand for various cardiovascular practices, the recruiters say the greatest demand is for general clinical work, then specialists. Academic positions (any blend of practice and research) are least in demand (Fig. 13).

For foreign-born IMGs to stay in the U.S., visa status is crucial for establishing a cardiovascular career. To help navigate U.S. visa and license options, IMGs need professional help to figure out the best ways to remain in the U.S. (Note: Medical schools and training programs may offer visa assistance or have an attorney on retainer.) For IMGs applying to come to or stay in the U.S., it is important to know the application process and get help from academic institutions that have advisors who can be important resources for IMGs.

In terms of career opportunities, most IMGs prefer careers in academic clinical medicine. Initially, IMGs might consider coming to the U.S. to do only research. Careers in biomedical research are widely available for physician scientists from abroad. Moreover, research experience may be an advantage when eventually interviewing for admission into a U.S. residency program. Also, universities, medical schools, and research institutions may offer visa assistance for research activities. Often these research opportunities lead to careers involving patient care. As another pathway into U.S. training, IMGs have entered into U.S. graduate schools to obtain U.S. specialty certification. (See Table 28, for an overview of visa options and requirements for each pathway.)

Under the research pathway that involves no patient care, one visa option is the H-1 that is sponsored by the employer. The North American Free Trade Agreement (NAFTA) also provides some benefits for trainees coming into the U.S. from other North American countries. International medical graduates coming to the U.S. to do research do not need other medical examinations or licenses, but they also cannot practice in the U.S.

For those coming through the training pathway, individuals attending U.S. medical schools are not considered IMGs. The J-1 visa has a two-year return requirement after training while the H-1 does not demand a return to the country of origin.

For academic clinical practice, an O-1 visa is available for individuals with stature or unusual achievements. In the past, this visa was relatively easy to obtain, but since September 11, 2001, it has been much more difficult to get.

Options after J-1 training include returning to the country of 212(e) obligation (i.e., the country that originally issued the Ministry of Health letter) for two years or leave the U.S. and return on another nonimmigrant visa, such as a NAFTA visa for Canadian or Mexican academic physicians or the O-1 Alien of Extraordinary Ability worker visa. Another option is to obtain a waiver of the 212(e) home rule by serving in an underserved area. The problem with obtaining such a waiver is few underserved areas have academic medical centers. The only real option is a career opening at a Veterans Affairs (VA) medical center; however, those positions are getting progressively scarcer.

Despite these limiting factors, Congress passed a bill in October 2004 renewing all J-1 visas. The bill allows physicians with these visas to stay in the U.S. if they agree to practice in an underserved community for three years. Each state will be allowed to grant 30 waivers per year, including 5 waivers for physicians practicing in areas not specifically deemed "underserved" by the Department of Health and Human Services. This option allows J-1 holders to stay in the U.S.; however, if these individuals are aiming for an academic career, having a J-1 waiver in an underserved area would delay this process for three years.

There are obviously many issues that IMGs have to overcome to get not only staff positions but also research grants. Most NIH grants are restricted to U.S. citizens or resident aliens, but there are some exceptions; RO1s are available for IMGs with either a faculty position or who are fourth-year level trainees. There is an NIH visiting pro-

gram, wherein some foreign nationals come to the NIH as a visiting faculty or under a visiting fellowship. Such individuals can stay at the NIH for a number of years without having visa or working issues to contend with. For most other grants, such as those from the American Heart Association, ACC, and others, there are no citizenship restrictions.

Conclusions. The IMGs wishing to stay and practice in the U.S., particularly in an academic center, need early professional immigration advice. Large medical centers usually have advisors who will help IMGs navigate through the system. There are workshops to educate foreign medical students, physicians-in-training, and faculty in finding training and career opportunities. There is indeed a shortage in the health care workforce in the U.S., particularly in cardiology and other medical specialties. Consequently, this is a topic of great importance not only for IMGs but for all cardiologists in the U.S. Therefore, we should be aware and supportive of legislation that will help IMGs to have access to information, training, and career opportunities in the U.S.

XXI. PANEL DISCUSSION: JUNIOR AND SENIOR INVESTIGATORS EXCHANGE

Valentin Fuster, MD, PhD, FACC (Zena and Michael A. Wiener Cardiovascular Institute and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center, New York, New York)

Robert O. Bonow, MD, FACC (Northwestern University Feinberg School of Medicine, Division of Cardiology, Northwestern Memorial Hospital, Chicago, Illinois)

Christine E. Seidman, MD (Harvard Medical School and the Cardiovascular Genetics Service, Brigham and Women's Hospital, Boston, Massachusetts)

Dr. Fuster: We have invited young investigators to join us in this panel discussion and we will let them introduce themselves.

Fellow: I am from the University of Minnesota. I was born and raised in England, attended medical school in Egypt, and came to the U.S. in 1998. I did my chief residency at Geisinger Medical Center, Penn State, and have been at the University of Minnesota for more than two years now. I am doing work in stem cell biology and received a National Research Service Award (NRSA) grant based on that work.

Ulrich Luft: I am Ulrich Luft from Oregon Health Sciences University (OHSU). I went to medical school at OHSU, did my residency at Stanford University, and then fast-tracked into cardiology back at OHSU. I'm in my second year of fellowship and am doing my first year of research. I received an American Heart Association postdoctoral fellowship grant award last year and have been doing research for the last six months on some vascular biology projects.

Dr. Fuster: Bob, tell us a little about your training.

Dr. Bonow: I started my career at the National Institutes of Health (NIH), going from residency to the Clinical Associate Program. That was back in 1976; it is no longer quite the same. The way to do that today might be for someone who has already had clinical training with or without research training to identify a possible mentor on the intramural side of the NIH. My mentor was Steve Epstein initially, and when I started telling people about what mentors can and should be, I always think of Steve. Along my career, and I think this is true for everybody of my vintage, you gain new mentors over time and at any one moment you may have more than one mentor.

Dr. Fuster: When you look forward, what do you plan to do in the next three years?

Fellow: I am committed to becoming an academic cardiologist. I am planning to take the results that I have from the NRSA grant and apply it to an NIH K08 or K23 award. The question for me is whether I am going to go with molecular biology or translational research, because stem cell biology is moving into translational science, at least here in the U.S. We are hoping that the work we are doing will move into the clinical trial setting within the next two to three years, so I see a very good opportunity for translational research in that area.

I will be applying for a junior faculty position within the next year and a half, and hopefully within the next year, I will be taking the data that I have and apply for a K23, and then take it to wherever I get my faculty position. One of the things I have learned is it's very hard to compete with PhD scientists in the laboratory, especially when you have big labs and especially when your mentor is a PhD, whose knowledge is much more extensive than yours. Right now, I think translational research involves just trying to find the right area that has the greatest potential to grow and then apply it to your own personal career.

Dr. Bonow: This may mean that your current mentor is very good for the basic research components, but as you move more to the translational side, to reiterate the point I was making a second ago, you may need to have more than one mentor.

Fellow: Absolutely, and I was very lucky that within the University of Minnesota, we started doing clinical work in the stem cell arena. So I have already doubled-up with another mentor who has started to do the clinical work.

One issue I want to raise here is that bench research has a well-defined training track. You go into the lab for two or three years, learn these techniques, and come out trained versus translational and clinical research, where the training track is, presently, less well defined. That is my current struggle, and that's what I want to discuss.

Dr. Fuster: If I were your mentor, I would do a little bit of psychoanalysis on you. I would say that you are probably more interested in the application of basic research, rather than basic research itself. Basic research is your tool, your methodology.

Dr. Bonow: There is an issue concerning the structural components of training in a clinical training program where there is some research involved. We are very good at teaching fellows how to push catheters, do echocardiograms, and hopefully, how to take care of patients. Beyond that, we are supposed to teach them clinical research, but too often we are asking them to learn that somehow through osmosis without any kind of didactic material. That's not gone unnoticed, and there are, indeed, programs now that have put a curriculum in place for clinical research training. The K12 and K30 awards do put structure in place for people who have interests in clinical trials, clinical trial design, bioethics, biostatistics, population studies, or outcomes research, and these awards go a long way toward helping you transition your current basic research into translational research.

Fellow: I agree with Dr. Fuster, who is saying that throughout your life as a junior investigator you learn several tools and then you try to apply these tools where your passion takes you. I knew my passion was translational research, but the tools that were available to learn at that time were more related to bench science research. I think we are starting to explore other avenues in other programs, in both translational and clinical, which is good. I am just raising a point that was brought up in several discussions that the training track for clinical and translational research is much less defined. There are institutions in the U.S. trying to take some initiative and train their people, but it's very institutional-dependent.

Dr. Fuster: Yes, but let us look at an example. I can have a rat heart that I think contains stem cells, and I want to know that there are several types of stem cells: some in the atrium, some in the ventricle, and so on. I want to take these different cells, transplant them to make them grow, and then transplant them into the rat again. What I am doing is somewhat translational, but it is all in the basic research area. It really seems that you are anxious to move the research to humans. But both, in a way, are translational. Dr. Luft, what about you?

Dr. Luft: Academic cardiology is my career track. I have a grant, and we are working on a very interesting project using vascular biology and cellular electrophysiology. That is where I have experience and did patch clamping for a few years before going to medical school. If our project is successful, I will hopefully get some decent papers out of it and then continue doing research and academic cardiology. My plan would be to apply for an NIH K08 award and hope to move from there to an R01. I think my expertise and passion lean more towards basic bench science as opposed to clinical investigation.

Dr. Bonow: We know that the K awards have been quite successful. But are they going to continue at the same level? Because the NIH budget is not increasing at the same level. A lot of the doubling of the NIH budget turned out to be mostly infrastructure. There are going to be fewer of the K awards and, historically, there have been a lower percentage of awards at the next level, the R01 awards. Do you see a solution here to maintain the investigator workforce at a high level of enthusiasm?

Dr. Fuster: Things have changed. If you had asked this question about 10 years ago, the answer probably would have been different. But, at this time, it is so important to be trained in a team environment; I think the K23 and the K18 are very important grants, because they really give you the motor engine of how to function in the future.

Dr. Bonow: The R01 has been the metric in the past for career advancement, but now we are talking more about team-based approaches to research. Right now, in most academic medical centers, academic advancement is still based on how many R01s you have. Consequently, many universities now are grappling with developing different promotion pathways based upon your contributions to research, which may not be measured by R01s.

Dr. Fuster: Program projects and grants are evolving to give opportunities to less senior people who want to contribute. I know a number of people for whom these programs and grants have been the entry to a successful career. There are more and more of these program projects and support for Continuous Research Excellence grants that are, relatively speaking, better funded now. Christine, can you comment on that?

Dr. Seidman: I tell people, "It is never too late to go into basic science or applied science or clinical science." That is something more of us as physicians must do because, otherwise, medicine will not advance. Whether it is a stem cell question or electrophysiology or how to make a better cath, it is profoundly important that you be invested in it. You certainly can change your career path at any time. It takes a bit of guts, and it often takes a hit to your income, but it is profoundly important and, I think, very rewarding.

With regard to R01s, I would unequivocally sanction the idea that team science and investigation is what's out there right now; there are no more single scientists. It's incredibly fun to be able to work with your PhD colleagues, using all your medical expertise, meaning that you're going to see things in a different perspective. For example, you may see questions more from a pathophysiologic perspective as compared to, perhaps, a mathematical modeling perspective. But when those two backgrounds intersect, what can happen is really an explosion of new knowledge. So, I would encourage you not to be worried about whether you fit, whether you understand all the terminology or whatnot—if there is a contribution you can make, do not be afraid to say it, and do not be afraid to contribute it; ask questions, learn, and be part of a team. Right now, science is moving at such an accelerated pace, there is nobody who knows everything.

Dr. Luft: I have a question that pertains to what we have been discussing. When I think about my career and how it might develop, I have to admit that when I originally started medicine, I figured I would go into academic medicine and become a research or clinical investigator. But as I do clinical cardiology, I find that it is really fun, and the more

clinical cardiology I do, the more I enjoy it. Most of us here probably enjoy pushing catheters and titrating drips. When I look at some of the descriptions given here of the physician scientist or the clinical investigator—80% of your time being spent in the lab, and so on—it seems a little disappointing. In fact, I had an attending who would put in bedside pacemakers and then go off to lab and do his bench science—he split his clinical and research time about 50/50—and was successful. Is there still a role for such a physician-scientist today, or do you basically have to decide: one or the other?

Dr. Fuster: It is not unusual to be research-oriented, which means that you are looking at the cause and effects and the process; it does not matter if you are dealing with a molecule, a cell, tissue, or a human being. I enjoy pathophysiology tremendously, but now I also enjoy what is happening with stem cells and trying to understand them, because the way I think is very similar to what you have described. I have seen basic investigators who are superb clinicians based on their thinking process. Therefore, I do not think what you are talking about is unusual, because it is pretty much the same principles.

Another thought relates to "What are you able to do at the same time?" If you spend 40% of your time in research, it will be difficult to be competitive with those who spend 90% of their time doing research. You might be able to do both in much the same way as many in my generation were able to do it. I was able to do it, too, for that matter; but today I look at what it is I did and realize it was very superficial. Because of the competitive nature of the world today, it is getting more and more difficult to really do research that is fundable when you spend just a small portion of time on it.

Dr. Bonow: Yes, cardiology is fun and saving lives is habit-forming; there is nothing wrong with choosing a career as a clinician. That is fine. Our role in the academic medical center is also to train the next generation of clinicians and clinician educators. Along the way though, some of those clinicians can also participate in clinical trials. But Dr. Fuster is absolutely right: you are going to be competing with other people who may be as bright as you are and they are spending 100% of their time in research. If you need to compete with them for the money to support the research you want to do, then you cannot dabble in it. It really does require focus and dedication. Perhaps at a later stage in your career you can broaden what you are doing.

Fellow: I want to make a comment about that. As much fun as cardiology is, it also is demanding in terms of technicalities. I was discussing this with Dr. Balke, and he said 35 years ago all he had to learn was catheterization and the angiogram; that was it. Today, there is a whole lot more to learn. I asked if he thought an interventional cardiologist in this modern age could be a clinician scientist. His honest opinion was "probably not," because of the number of procedures that an interventionalist has to do to retain not just certification but competency in order to be on the same level as his colleagues.

Also, I want to talk about the concept of the team. You have got the PhD scientists and clinicians working together. The funding is in the name of the PhD scientist. This raises another problem, in that it appears a lot of universities tend to promote those individuals doing basic research before those who are doing research and clinical work. I think this endangers this concept of a team, because if team members are not credited with their work and earn the promotions, then people are going to just lose interest.

I think the technical demands are too much right now for us to keep up. I do not have a solution for that. You have to compromise and you have to prioritize, personally, to get to where you want. But institutions and chiefs of cardiology have to think about this whole concept of promotion, what it is based on, whether it is a team approach or individual, and whether the money you get for research is what you are going to be judged on.

Dr. Fuster: I can only tell you things are changing, because institutions are finding that great clinicians and teachers are leaving because they are not being promoted. Therefore, there is a lot of pressure to change the guidelines of promotion. There is a new line, which is the teacher clinician, and their numbers are growing because of the pressure created for institutions to really maintain people who are very necessary for survival of the institutions. So, this is indeed changing in a very positive way.

Dr. Seidman: I agree with that. The promotions criteria are under active review in virtually every institution that has not yet executed the changes, and you shouldn't make a career decision based on those potential problems. Anybody who has been through any training program for a medical degree knows that the rules are always changing as you go along. That is the nature of the game.

With regard to whether you can be part clinician/part researcher—for example, do invasive cardiology and research—and the answer is, unequivocally, yes. That is what defines an academician as compared to a private practitioner, but it doesn't mean that you are doing the same science as a PhD-trained individual who spends 100% of his time in a wet lab.

There is no better time to do clinical research. You can do basic fundamental genetic molecular biology, transcriptional biology, and so on, on people. It is simply a matter of what format you are going to structure that in. Can it be done in the cath lab? Absolutely—it is right now. If you want to devote 50% of your time doing clinical care of patients, call it private practice, you are not going to be as successful in the funding arena. It is not that you're not doing anything. It just means that you are going to have a different mechanism by which you accomplish all that you want to do.

Dr. Fuster: That is an important point. The sense of success is fulfillment, and although you may not necessarily be publishing in *Cell* or *Journal of Clinical Investigation* or *Science*, you may be able to do work that gets published in

very good journals and be very instrumental in changing medicine. You might not be as fundable as some other investigator, but you still can enjoy and contribute to science.

Dr. Bonow: I agree. If you pick up *Circulation* and *Journal of the American College of Cardiology*, most of the papers written there do change practice and have immediate application to what you are going to do tomorrow with your patients. They are not written necessarily by tenure-track faculty with R01s, but if they are putting paper after paper in *Circulation* and *Journal of the American College of Cardiology*, they are going to get promoted. So, I disagree that the clinician scientist has a different likelihood of promotion than the basic scientist. It really depends on productivity, and there are other kinds of faculty, too, who are more clinician educators who rarely publish. Their job is to see patients and teach, and they are on a totally different career trajectory, and their grounds for promotion differ.

Fellow: There is a trend that you are all aware of: the private, not-for-profit institutions that are funding mainly clinical and maybe some translational research. It is well known that these nonprofit organizations offer better salaries than traditional university settings, and a lot of people go there, and many of them mentor people like us. If these places have the funds and the infrastructure for clinical research, what do you think about this option?

Dr. Bonow: I do not think that there are that many institutes like what you describe; most people go into practice. Yes, you will get paid more in practice, but it is very busy and it's not easy because reimbursement is dropping. There is a lot of competition, which means you have to do more to keep your head above water. Most people that go into practice do not already have a hugely successful academic career before going there; consequently, going in at the entry level into a practice like that makes it unlikely you'll achieve that level of stardom. When things get tough and reimbursement continues to fall, that's probably the first thing that's going to be cut off the agenda.

Dr. Seidman: Do not you want to be in a place where discoveries can be translated? Do not you want to hear that some mathematician has a new model that allows you to look at geometry of the ventricle and what better place to try it out than in the echo lab? To me, the team approach is superior. And when I say team, I do not just mean the people you work with specifically, because communications have made us all closer around the world and you can collaborate with anyone. There is nothing like bumping into the person next door and coming up with a great experiment, because he or she is going in one trajectory and you have intersected in a different way. That's the advantage of an academic community, and I would say that a university system is second to none in that environment.

Dr. Fuster: There are exceptions, though, when it comes to some private institutes. For example, the Cancer and Heart Institute started very private, and they have an incredible research group in diabetes now. But, it's not the same academic environment and the excitement that we are talking about. There are significant differences.

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